



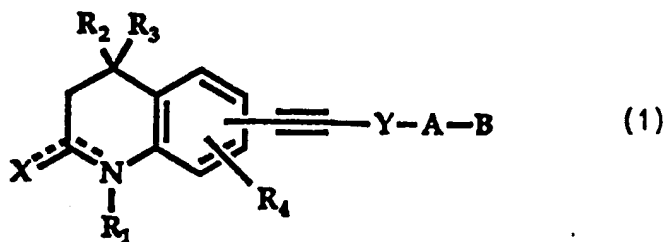
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 215/22, A61K 31/47, C07D 215/36		A1	(11) International Publication Number: WO 96/36609
		(43) International Publication Date: 21 November 1996 (21.11.96)	
(21) International Application Number: PCT/US96/06866 (22) International Filing Date: 13 May 1996 (13.05.96) (30) Priority Data: 08/442,223 16 May 1995 (16.05.95) US (71) Applicant: ALLERGAN [US/US]; 8301 Mars Drive, Waco, TX 76712 (US). (72) Inventors: TENG, Min; 2 Dove Street, Aliso Viejo, CA 92656 (US). BEARD, Richard, L.; 2341 Azure Avenue, Newport Beach, CA 92660 (US). COLON, Diana; 247 Veneto, Irvine, CA 92714 (US). DUONG, Tien, T.; Apartment 15C, 13 Bearpaw, Irvine, CA 92714 (US). CHANDRARATNA, Roshantha, A.; 25841 Empresa, Mission Viejo, CA 92691 (US). (74) Agents: BARAN, Robert, J. et al.; Allergan, Inc., 2525 Dupont Drive, T-22-E, P.O. Box 19534, Irvine, CA 92713-9534 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report.	

(54) Title: QUINOLYL-ETHYNYL DERIVATIVES HAVING RETINOID-LIKE ACTIVITY

(57) Abstract

Compounds of formula (1) where the dotted lines represent a bond or the absence of a bond; R₁ is H, lower alkyl of 1 to 10 carbons, lower alkenyl of 2 to 10 carbons, phenyl C₁-C₆ lower alkyl, phenyl C₂-C₆ lower alkenyl, heteroaryl C₁-C₆ lower alkyl, heteroaryl C₂-C₆ lower alkenyl, or R₁ is



absent; X is S, R₅S or R₅O where R₅ is lower alkyl of 1 to 10 carbons, lower alkenyl of 2 to 10 carbons, phenyl C₁-C₆ lower alkyl, phenyl C₂-C₆ lower alkenyl, heteroaryl C₁-C₆ lower alkyl, heteroaryl C₂-C₆ lower alkenyl, with the proviso that when R₁ is H then X is S; R₂ and R₃ are hydrogen, lower alkyl of 1-6 carbons, or halogen; R₄ is hydrogen, lower alkyl of 1-6 carbons, halogen, OR₁₁, SR₁₁, OCOR₁₁, SCOR₁₁, NH₂, NHR₁₁, N(R₁₁)₂, NHCOR₁₁ or NR₁₁COR₁₁; Y is phenyl or a heteroaryl group selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl and oxazolyl; A is (CH₂)_n where n is 0-5, lower branched chain alkyl having 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6 carbons and 1 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2 triple bonds; B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, COOR₈, CONR₉R₁₀, -CH₂OH, CH₂OR₁₁, CH₂OCOR₁₁, CHO, CH(OR₁₂)₂, CHOR₁₃O, -COR₇, CR₇(OR₁₂)₂, or CR₇OR₁₃O, where R₇ is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R₈ is an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R₈ is phenyl or lower alkylphenyl, R₉ and R₁₀ independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R₁₁ is lower alkyl, phenyl or lower alkylphenyl, R₁₂ is lower alkyl, and R₁₃ is divalent alkyl radical of 2-5 carbons, have retinoid-like biological activity.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

QUINOLYL-ETHYNYL DERIVATIVES HAVING RETINOID-LIKE ACTIVITY

5

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention is directed to novel compounds which have retinoid-like biological activity. More specifically, the present invention relates to ethyne compounds which have a phenyl or a heteroaryl substituent and also a 2-thio-1,2,3,4-tetrahydroquinolinyl, 2-alkylthio-1,2,3,4-tetrahydroquinolinyl or 2-alkoxy-1,2,3,4-tetrahydroquinolinyl substituent. The phenyl or heteroaryl group may have an acid or ester function, which may also be converted to an alcohol, aldehyde or ketone, or derivatives thereof, or may be reduced to -CH₃.

20

3. Related Art

Compounds which have retinoid like activity are well known in the art, and are described in numerous United States and foreign patents and in scientific publications. It is generally known and accepted in the art that retinoid-like activity is useful for treating animals of the mammalian species, including humans, for curing or alleviating the symptoms and conditions of numerous diseases and conditions. In other words, it is generally accepted in the art that pharmaceutical compositions having a retinoid-like compound or compounds as the active ingredient are useful as regulators of cell proliferation and differentiation, and particularly as agents for

30

treating dermatoses, such as acne, Darier's disease, psoriasis, ichthyosis, eczema and atopic dermatitis, and for treating and preventing malignant hyperproliferative diseases such as epithelial cancer, breast cancer, prostatic cancer, head and neck cancer and myeloid leukemias, for reversing and preventing atherosclerosis and restenosis resulting from neointimal hyperproliferation, for treating and preventing other non-malignant hyperproliferative diseases such as endometrial hyperplasia, benign prostatic hypertrophy, proliferative vitreal retinopathy and dysplasias, for treating autoimmune diseases and immunological disorders (e.g. lupus erythematosus) for treating chronic inflammatory diseases such as pulmonary fibrosis, for treating and preventing diseases associated with lipid metabolism and transport such as dyslipidemias, for promoting wound healing, for treating dry eye syndrome and for reversing and preventing the effects of sun damage to skin.

United States Patent No. 4,810,804 discloses such disubstituted acetylene compounds wherein one of the substituents of the acetylene group is a substituted phenyl group, and the second substituent is substituted or unsubstituted 6-chromanyl, 6-thiochromanyl or 6-tetrahydroquinolinyl group. The compounds disclosed and claimed in United States Patent No. 4,810,804 have retinoid acid-like biological activity.

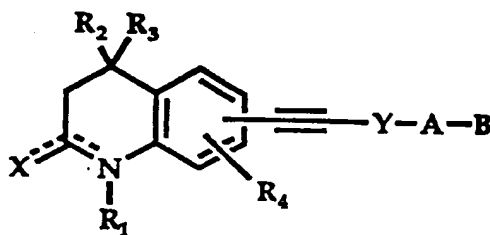
A published European patent application of the present applicant (Publication No. 0284288, published on September 28, 1988) describes compounds having retinoic acid-like activity which are 4,4-disubstituted 6-chromanyl, 4,4-disubstituted 6-thiochromanyl and 4,4-

disubstituted 6-tetrahydroquinolinyl acetylenes also substituted by a substituted heteroaryl group.

United States Patent Nos. 5,013,744, 5,023,341, 5,053,523, and 5,089,509 describe ethyne compounds substituted with a heteroaromatic or monocyclic aromatic substituent and also with a second monocyclic aromatic or heteroaromatic substituent. United States Patent No. 5,399,561 describes ethyne compounds which have a phenyl or a heteroaryl substituent and also a 2-oxochromanyl, 2-oxothiochromanyl or 2-oxo-1,2,3,4-tetrahydroquinolinyl substituent. The compounds described in these patents have retinoid-like biological activity. Numerous further United States patents and applications for patent assigned to the same assignee as the present invention, are directed to compounds having retinoid-like biological activity.

SUMMARY OF INVENTION

The present invention relates to compounds of Formula 1



Formula 1

where the dotted lines represent a bond or the absence of a bond;

R_1 is H, lower alkyl of 1 to 10 carbons, lower alkenyl of 2 to 10 carbons, phenyl $C_1 - C_6$ lower alkyl,

phenyl C₂ - C₆ lower alkenyl, heteroaryl C₁ - C₆ lower alkyl, heteroaryl C₂ - C₆ lower alkenyl, or R₁ is absent;

5 X is S or O, R₅S or R₅O where R₅ is lower alkyl of 1 to 10 carbons, lower alkenyl of 2 to 10 carbons, phenyl C₁ - C₆ lower alkyl, phenyl C₂ - C₆ lower alkenyl, heteroaryl C₁ - C₆ lower alkyl, heteroaryl C₂ - C₆ lower alkenyl, with the proviso that when R₁ is H then X is S;

10 R₂ and R₃ are hydrogen, lower alkyl of 1 - 6 carbons, or halogen;

R₄ is hydrogen, lower alkyl of 1 - 6 carbons, halogen, OR₁₁, SR₁₁, OCOR₁₁, SCOR₁₁, NH₂, NHR₁₁, N(R₁₁)₂, NHCOR₁₁ or NR₁₁COR₁₁;

15 Y is phenyl or a heteroaryl group selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, imidazolyl and oxazolyl;

20 A is (CH₂)_n where n is 0-5, lower branched chain alkyl having 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6 carbons and 1 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2 triple bonds;

25 B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, COOR₈, CONR₉R₁₀, -CH₂OH, CH₂OR₁₁, CH₂OCOR₁₁, CHO, CH(OR₁₂)₂, CHOR₁₃O, -COR₇, CR₇(OR₁₂)₂, or CR₇OR₁₃O, where R₇ is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R₈ is an alkyl group of 1 to 10 carbons, or a
30 cycloalkyl group of 5 to 10 carbons, or R₈ is phenyl or lower alkylphenyl, R₉ and R₁₀ independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower

alkylphenyl, R_{11} is lower alkyl, phenyl or lower alkylphenyl, R_{12} is lower alkyl, and R_{13} is divalent alkyl radical of 2-5 carbons.

In a second aspect, this invention relates to the use of the compounds of Formula 1 as regulators for cell proliferation and differentiation, and particularly as agents for treating dermatoses, such as acne, Darier's disease, psoriasis, ichthyosis, eczema, atopic dermatitis, and for treating and preventing malignant hyperproliferative diseases such as epithelial cancer, breast cancer, prostatic cancer, head and neck cancer and myeloid leukemias, for reversing and preventing arteriosclerosis and restenosis resulting from neointimal hyperproliferation, for treating and preventing other non-malignant hyperproliferative diseases such as endometrial hyperplasia, benign prostatic hypertrophy, proliferative vitreal retinopathy and dysplasias, for treating autoimmune diseases and immunological disorders (e.g. lupus erythematosus), for treating chronic inflammatory diseases such as pulmonary fibrosis, for treating and preventing diseases associated with lipid metabolism and transport such as dyslipidemias, for promoting wound healing, for treating dry eye syndrome and in reversing and preventing the effects of sun damage to skin.

This invention also relates to a pharmaceutical composition comprising a compound of Formula 1 in admixture with a pharmaceutically acceptable excipient.

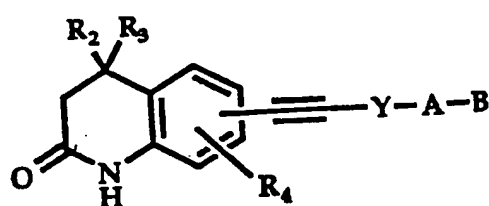
In another aspect, this invention relates to the process for making a compound of Formula 1, which process comprises:

reacting a compound of Formula 2 with an

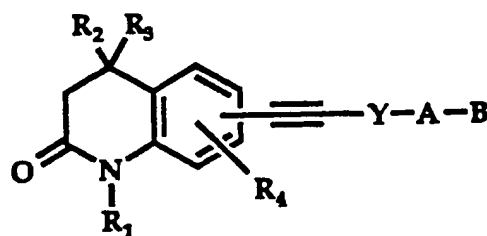
alkylating or alkenylating agent of the formula R_5-Z (Z is a leaving group, such as I) to obtain a compound of Formula 1 where R_1 is absent and X is R_5O ; or

reacting a compound of Formula 3 with a thiolyating agent (such as Lawesson's reagent) to obtain a compound of Formula 1 where X is S; or

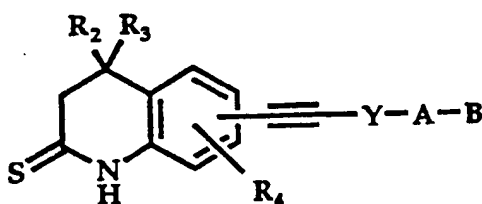
reacting a compound of Formula 4 with an alkylating or alkenylating agent of the formula R_5-Z to obtain a compound of Formula 1 where R_1 is absent and X is R_5S . In Formulas 2, 3 and 4 the symbols are defined the same as in connection with Formula 1.



Formula 2



Formula 3



Formula 4

Still further the present invention relates to the processes of homologating a compound of Formula 1 where A is $(CH_2)_n$ and n is 0-4 to give an acid of Formula 1; or

- 5 converting an acid of Formula 1 to a salt; or
 forming an acid addition salt;
 converting an acid of Formula 1 to an ester; or
 converting an acid of Formula 1 to an amide; or
 reducing an acid of Formula 1 to an alcohol or
10 aldehyde; or
 converting an alcohol of Formula 1 to an ether or
 ester; or
 oxidizing an alcohol of Formula 1 to an aldehyde;
 or
15 converting an aldehyde of Formula 1 to an acetal;
 or
 converting a ketone of Formula 1 to a ketal.

DETAILED DESCRIPTION OF THE INVENTION

General Embodiments

20 Definitions

 The term alkyl refers to and covers any and all groups which are known as normal alkyl, branched-chain alkyl and cycloalkyl. The term alkenyl refers to and covers normal alkenyl, branch chain alkenyl and
25 cycloalkenyl groups having one or more sites of unsaturation. Unless stated otherwise in these specifications lower alkyl means the above-defined broad definition of alkyl groups having 1 to 6 carbons, and as applicable, 3 to 6 carbons for branch chained
30 and cyclo-alkyl groups. Lower alkenyl is defined similarly having 2 to 6 carbons for normal alkenyl, and 3 to 6 carbons for branch chained and cycloalkenyl groups.

The term "ester" as used here refers to and covers any compound falling within the definition of that term as classically used in organic chemistry. It includes organic and inorganic esters. Where B (of Formula 1) is -COOH, this term covers the products derived from treatment of this function with alcohols or thioalcohols preferably with aliphatic alcohols having 1-6 carbons. Where the ester is derived from compounds where B is -CH₂OH, this term covers compounds derived from organic acids capable of forming esters including phosphorous based and sulfur based acids, or compounds of the formula -CH₂OCOR₁₁ where R₁₁ is defined as above.

The term "amides" has the meaning classically accorded that term in organic chemistry. In this instance it includes the unsubstituted amides and all aliphatic and aromatic mono- and di- substituted amides.

A pharmaceutically acceptable salt may be prepared for any compounds in this invention having a functionality capable of forming such salt, for example an acid functionality. A pharmaceutically acceptable salt is any salt which retains the activity of the parent compound and does not impart any deleterious or untoward effect on the subject to which it is administered and in the context in which it is administered.

Pharmaceutically acceptable salts may be derived from organic or inorganic bases. The salt may be a mono or polyvalent ion. Of particular interest are the inorganic ions, sodium, potassium, calcium, and magnesium. Organic salts may be made with amines, particularly ammonium salts such as mono-, di- and

trialkyl amines or ethanol amines. Salts may also be formed with caffeine, tromethamine and similar molecules. Where there is a nitrogen sufficiently basic as to be capable of forming acid addition salts, such may be formed with any inorganic or organic acids or alkylating agent such as methyl iodide. Preferred salts are those formed with inorganic acids such as hydrochloric acid, sulfuric acid or phosphoric acid. Any of a number of simple organic acids such as mono-, di- or tri- acid may also be used.

The compounds of the present invention may contain one or more double bonds, and therefore may have trans and cis (E and Z) isomers. In addition, the compounds of the present invention may contain one or more chiral centers and therefore exist in enantiomeric and diastereomeric forms. The scope of the present invention is intended to cover all such isomers per se, as well as mixtures of cis and trans isomers, mixtures of diastereomers and racemic mixtures of enantiomers (optical isomers) as well.

With reference now to **Formula 1**, the preferred compounds of this invention are those where Y is phenyl, pyridyl, thienyl or furyl, with the phenyl derivatives being particularly preferred. When Y is phenyl, compounds are preferred where the ethynyl group and the A-B group are attached to the 1 and 4 positions respectively of a benzene ring (i.e., where the phenyl moiety of the compound is para substituted). When the Y group is pyridyl, thienyl or furyl, compounds are preferred where the ethynyl group and the A-B group are attached to the 2 and 5 positions respectively of a pyridine ring (the 6 and 3 positions of the nicotinic acid nomenclature being equivalent to the 2/5

designation in the pyridine nomenclature) or to the 5 and 2 positions respectively of a thiophene or furan group, respectively. Compounds where Y is phenyl, and where the phenyl group is para substituted in the
5 above-described manner, are particularly preferred.

The ethynyl group is preferably attached to the 6 or to the 7 position of the quinoline nucleus.

With regard to the A-B side chain (substituent) on the phenyl or heteroaryl group Y, compounds are
10 preferred where A is $(CH_2)_n$ and n is 0. With regard to group B, compounds are preferred where B is $-COOH$, an alkali metal salt or organic amine salt, or a lower alkyl ester thereof.

Regarding the substituents R_2 and R_3 , compounds
15 are preferred where these substituents are lower alkyl of 1 to 6 carbons, most preferably methyl.

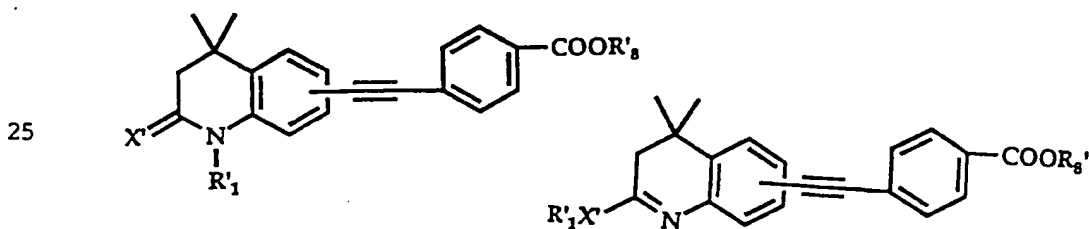
The R_4 substituent is preferably H or lower alkyl of 1 to 6 carbons, even more preferably H or CH_3 . Moreover, the R_4 group is preferably attached to the
20 otherwise unoccupied 6 or 7 position of the quinoline nucleus.

Referring now to the R_1 group of the compounds of the invention in accordance with Formula 1, the preferred compounds are where R_1 is H, lower alkyl of 1
25 to 10 carbons, including branch chained lower alkyl, or benzyl.

When X is R_5S or R_5O , then R_5 is preferably lower alkyl of 1 to 10 carbons, including branch chained lower alkyl.

30 The most preferred compounds of the invention are shown in Table 1 with reference to Formula 5 and Formula 6.

		Table					1
Compound #	Formula	position of \equiv on quinoline nucleus	X'	R' ₁	R' ₈		
5	5	5	6	O	i-propyl	ethyl	
	6	6	6	O	i-propyl	ethyl	
	7	5	6	S	i-propyl	ethyl	
	8	5	6	S	H	ethyl	
	9	6	6	S	methyl	ethyl	
10	10	6	6	S	n-heptyl	ethyl	
	11	6	6	O	i-propyl	H	
	12	5	6	S	i-propyl	H	
	13	5	6	S	H	H	
	14	6	6	S	methyl	H	
	15	6	6	S	n-heptyl	H	
	22	5	7	S	H	ethyl	
	23	6	7	S	methyl	ethyl	
	28	6	7	O	i-propyl	ethyl	
	31	5	7	O	i-propyl	ethyl	
15	32	5	7	S	i-propyl	ethyl	
	33	5	7	S	H	H	
	34	6	7	S	methyl	H	
	35	6	7	O	i-propyl	H	
	36	5	7	S	i-propyl	H	
	37	5	6	O	benzyl	ethyl	
	38	5	6	O	n-heptyl	ethyl	
	39	5	6	O	benzyl	H	
20	40	5	6	O	n-heptyl	H	



30 The compounds of this invention may be administered systemically or topically, depending on such considerations as the condition to be treated, need for site-specific treatment, quantity of drug to be administered, and numerous other considerations.

In the treatment of dermatoses, it will generally be preferred to administer the drug topically, though in certain cases such as treatment of severe cystic acne or psoriasis, oral administration may also be used. Any common topical formulation such as a solution, suspension, gel, ointment, or salve and the like may be used. Preparation of such topical formulations are well described in the art of pharmaceutical formulations as exemplified, for example, Remington's Pharmaceutical Science, Edition 17, Mack Publishing Company, Easton, Pennsylvania. For topical application, these compounds could also be administered as a powder or spray, particularly in aerosol form. If the drug is to be administered systemically, it may be confectioned as a powder, pill, tablet or the like or as a syrup or elixir suitable for oral administration. For intravenous or intraperitoneal administration, the compound will be prepared as a solution or suspension capable of being administered by injection. In certain cases, it may be useful to formulate these by injection. In certain cases, it may be useful to formulate these compounds in suppository form or as extended release formulation for deposit under the skin or intramuscular injection.

Other medicaments can be added to such topical formulation for such secondary purposes as treating skin dryness; providing protection against light; other medications for treating dermatoses; medicaments for preventing infection, reducing irritation, inflammation and the like.

Treatment of dermatoses or any other indications known or discovered to be susceptible to treatment by retinoid-like compounds will be effected by

administration of the therapeutically effective dose of one or more compounds of the instant invention. A therapeutic concentration will be that concentration which effects reduction of the particular condition, or
5 retards its expansion. In certain instances, the compound potentially may be used in prophylactic manner to prevent onset of a particular condition. A useful therapeutic or prophylactic concentration will vary from condition to condition and in certain instances
10 may vary with the severity of the condition being treated and the patient's susceptibility to treatment. Accordingly, no single concentration will be uniformly useful, but will require modification depending on the particularities of the disease being treated. Such
15 concentrations can be arrived at through routine experimentation. However, it is anticipated that in the treatment of, for example, acne, or similar dermatoses, that a formulation containing between 0.01 and 1.0 milligrams per milliliter of formulation will
20 constitute a therapeutically effective concentration for total application. If administered systemically, an amount between 0.01 and 5 mg per kg per day of body weight would be expected to effect a therapeutic result in the treatment of many diseases for which these
25 compounds are useful.

 The retinoid-like activity of these compounds is confirmed through the classic measure of retinoic acid activity involving the effects of retinoic acid on ornithine decarboxylase. The original work on the
30 correlation between retinoic acid and decrease in cell proliferation was done by Verma & Boutwell, Cancer Research, 1977, 37,2196-2201. That reference discloses that ornithine decarboxylase (ODC) activity increased

precedent to polyamine biosynthesis. It has been established elsewhere that increases in polyamine synthesis can be correlated or associated with cellular proliferation. Thus, if ODC activity could be inhibited, cell hyperproliferation could be modulated. Although all causes for ODC activity increases are unknown, it is known that 12-0-tetradecanoylphorbol-13-acetate (TPA) induces ODC activity. Retinoic acid inhibits this induction of ODC activity by TPA. An assay essentially following the procedure set out in Cancer Res: 1662-1670, 1975 may be used to demonstrate inhibition of TPA induction of ODC by compounds of this invention. The results of this assay for certain exemplary compounds of the invention are shown in Table 2 below. IC₈₀ is that concentration of the test compound (expressed in nanomolar (nmol)) which results in 80 per cent inhibition of the ODC induction activity by TPA.

Table 2

Compound #	IC ₈₀ (nanomolar)
5	6.4
6	>100
7	5.5
8	54
9	29
10	>60
22	6.0
31	2.9
32	0.2
38	>100

SPECIFIC EMBODIMENTS**Synthetic Processes for Preparing Compounds of the Invention**

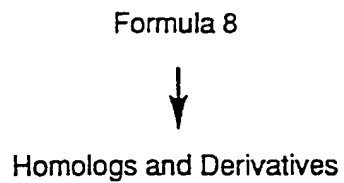
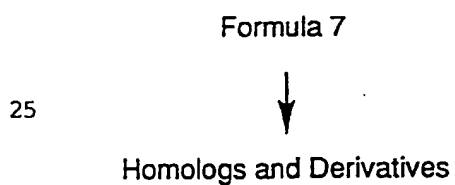
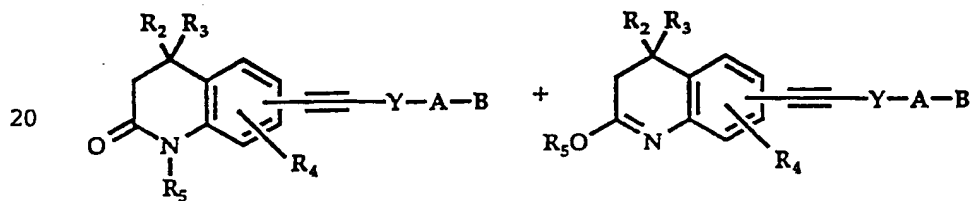
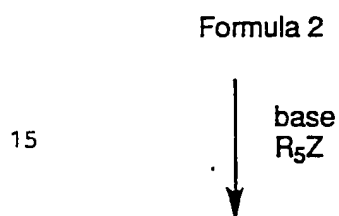
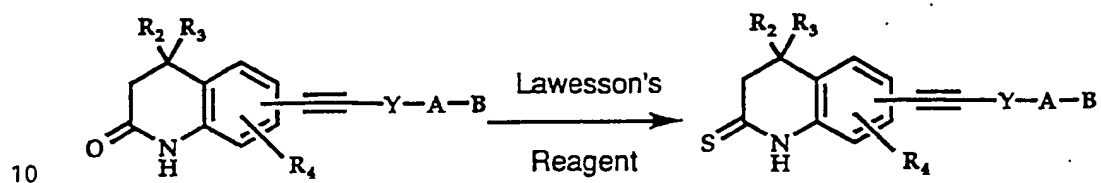
The compounds of this invention can be made by a number of different synthetic chemical pathways. To

illustrate this invention, there is here outlined a series of steps which have been proven to provide the compounds of **Formula 1** when such synthesis is followed in fact and in spirit. The synthetic chemist will
5 readily appreciate that the conditions set out here are specific embodiments which can be generalized to any and all of the compounds represented by **Formula 1**. Furthermore, the synthetic chemist will readily appreciate that the herein described synthetic steps
10 may be varied and/or adjusted by those skilled in the art without departing from the scope and spirit of the invention.

Broadly speaking, compounds of the present invention are prepared from compounds of **Formula 2**, as
15 this formula is defined above. Compounds of **Formula 2** are 2-oxo-1,2,3,4-tetrahydroquinoline derivatives which are substituted in the 6 or 7 position with an arylethynyl or heteroarylethynyl group. Compounds of **Formula 2** can be obtained in accordance with the
20 teachings of United States Patent No. 5,399,561 the specification of which is expressly incorporated herein by reference. Specifically, formula 42 in Column 17 of said reference patent discloses 6-aryl or 6-heteroaryl substituted 2-oxo-1,2,3,4-tetrahydroquinoline
25 derivatives which are suitable as starting materials for synthesis of compounds of the present invention and which are encompassed by **Formula 2** of the instant description. Formula 49 in Column 19 of said reference patent discloses 7-aryl or 7-heteroaryl substituted 2-
30 oxo-1,2,3,4-tetrahydroquinoline derivatives which are suitable as starting materials for synthesis of compounds of the present invention and which are also encompassed by **Formula 2** of the instant description.

16

5



30

17

5

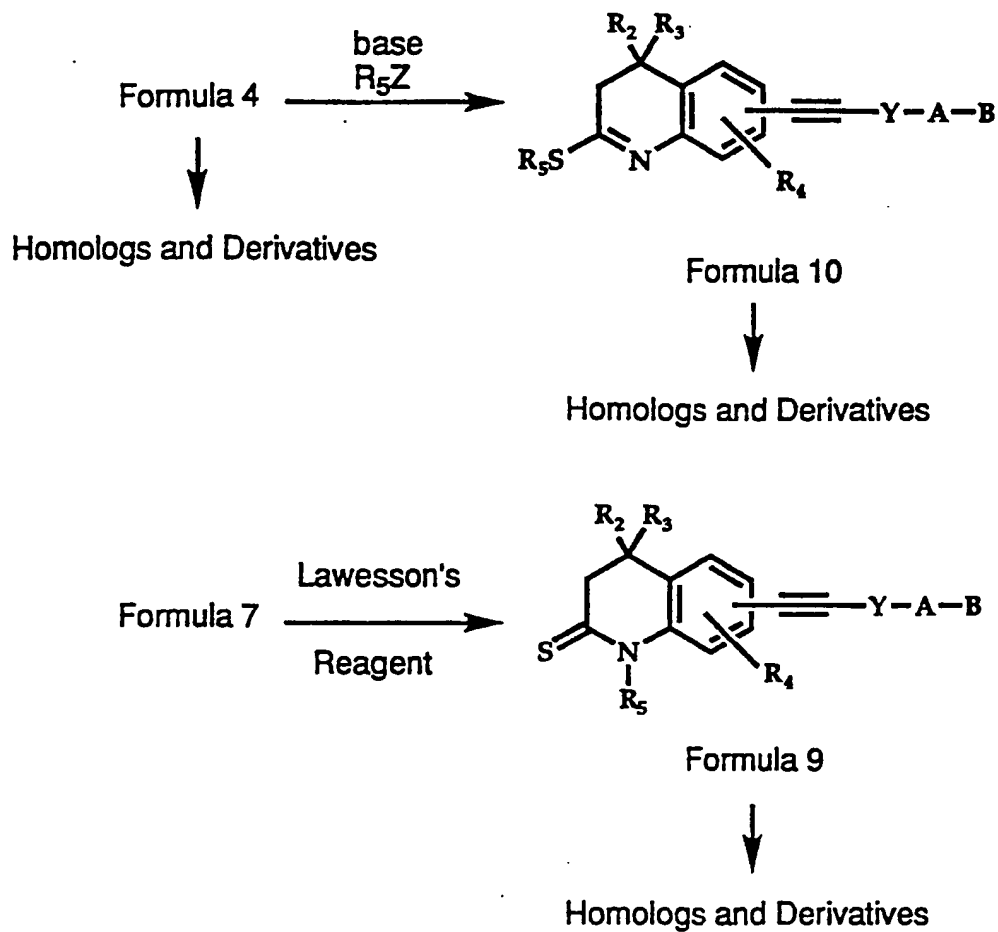
10

15

20

25

30



Reaction Scheme 1

Referring now to **Reaction Scheme 1** of the instant description, compounds of **Formula 2** are treated with base and a reagent R_5-Z . The group R_5 of the reagent is defined as in connection with **Formula 1**, typically

5 R_5 is an alkyl, alkenyl, aryl-alkyl or heteroaryl-alkyl group. Z is a leaving group which renders the R_5-Z reagent an "alkylating agent", Z is typically halogen, preferably bromine or iodine. Examples for the alkylating agent used for the preparation of the

10 compounds of the present invention are methyl iodide, isopropyl iodide, n-heptyl iodide and benzyl bromide. The alkylation reaction is typically conducted in an aprotic polar solvent such as dimethylformamide in the presence of strong base, such as sodium hydride. The

15 alkylation reaction typically provides a mixture of N-alkylated and O-alkylated products, that is compounds shown by **Formula 7** and **Formula 8** in the reaction scheme. These compounds can be separated from one another by conventional techniques, for example by

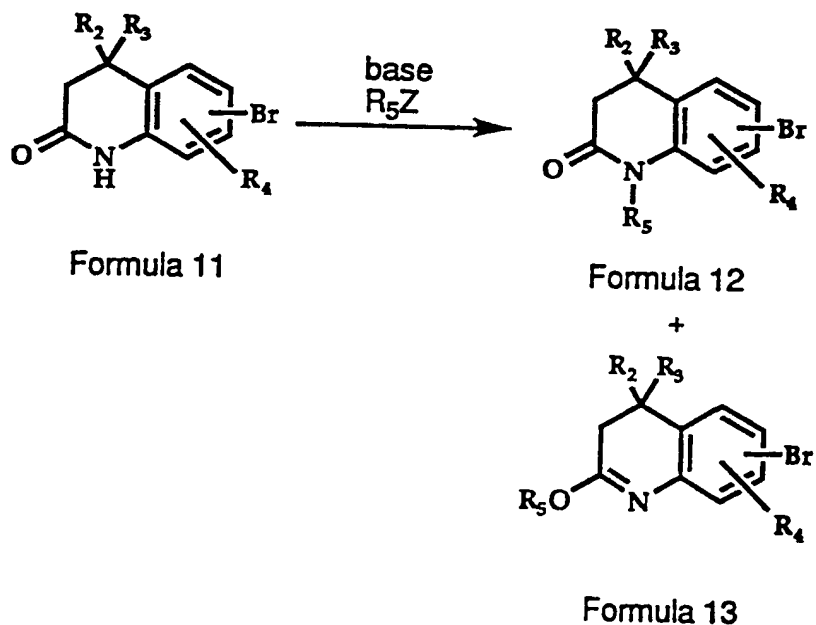
20 chromatography. Compounds of **Formula 7** are N-alkylated or alkenylated etc. derivatives. Compounds of **Formula 8** are 2-O-alkylated or alkenylated etc. derivatives. Compounds of **Formula 7** as well as compounds of **Formula 8** can be converted into "homologs and derivatives"

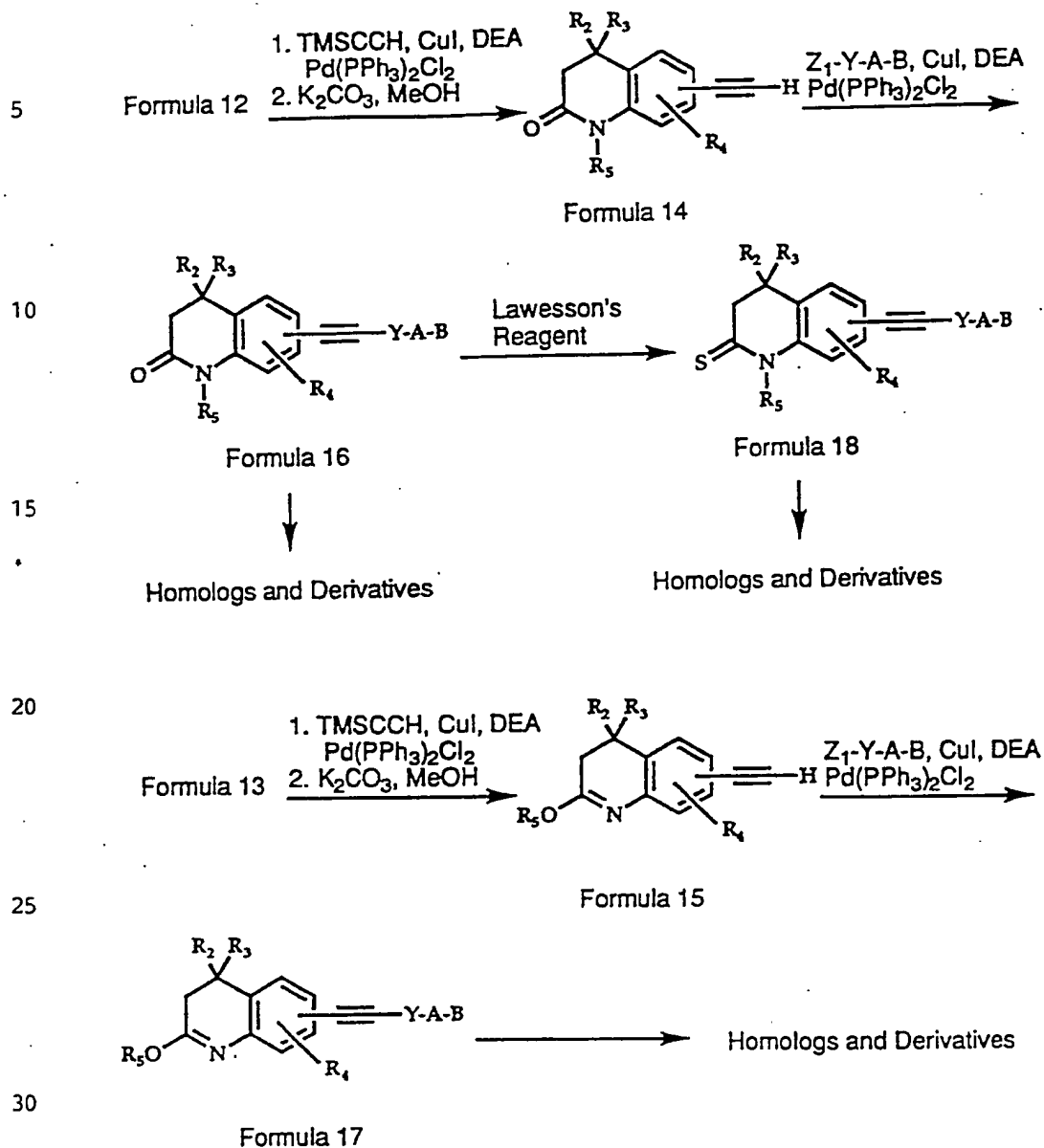
25 which are still within the scope of the present invention. Conversion to such "homologs and derivatives" may involve transformation of the **A-B** functionality, for example by saponification of an ester group, by formation of an amide or by

30 homologation of an acid or ester. These and other related transformations are described below.

Referring still to **Reaction Scheme 1**, the 2-oxo function of the 1,2,3,4-tetrahydroquinoline moiety of

the compounds of Formula 7 is converted to a thio group by a suitable "thiolating" reagent, typically and preferably with Lawesson's reagent. The latter reaction is typically conducted in a hydrocarbon solvent with moderate heating, preferably in benzene under refluxing conditions. The "thiolation" reaction provides compounds of Formula 9 wherein the R_5 is other than hydrogen. The compounds of Formula 2 can also be subjected to thiolation, preferably with Lawesson's reagent under conditions such as described above, to provide compounds of Formula 4 within the scope of the present invention. Compounds of Formula 4 are reacted with the "alkylating agent R_5-Z ", typically in an inert ether-type solvent such as tetrahydrofuran, in the presence of strong base, such as sodium hydride, to provide the S -alkylated derivatives of Formula 10, within the scope of the present invention.





Referring now to **Reaction Scheme 2**, another synthetic scheme suitable for the synthesis of the compounds of the present invention is disclosed. In accordance with this scheme, a 6-bromo- or a 7-bromo-2-oxoquinoline derivative of **Formula 11** is reacted with the alkylating agent R_5-Z to yield the corresponding N-alkylated derivative of **Formula 12** plus the corresponding O-alkylated derivative of **Formula 13**. A specific example of the starting materials in accordance with **Formula 11** of the instant description is 4,4-dimethyl-6-bromo-2-oxo-1,2,3,4-tetrahydroquinoline which is described in Column 24 of the referenced United States Patent 5,399,561. Another specific example of the starting materials in accordance with **Formula 11** of the instant description is 4,4-dimethyl-7-bromo-2-oxo-1,2,3,4-tetrahydroquinoline the preparation of which is described in the experimental section of the present specification. The N and O alkylated bromo compounds of **Formula 12** and **Formula 13** can be converted into the corresponding 6- or 7- ethynyl derivatives (**Formulas 14** and **15** in **Reaction Scheme 2**), and thereafter into the corresponding 6- or 7-arylethynyl or 6- or 7-heteroarylethynyl derivatives (**Formulas 16** and **17** in **Reaction Scheme 2**) substantially in accordance with the teaching of United States Patent No. 5,399,561, and specifically as is shown in Columns 17 and 18 in **Reaction Scheme 6** of that reference patent for the conversion of formula 38 to formula 42 in the reference. In summary, these transformations proceed through introduction of a (trimethylsilyl)acetylene group in place of the bromo function by coupling with (trimethylsilyl)acetylene in the presence of cuprous

iodide and a suitable catalyst, typically having the formula $\text{Pd}(\text{PQ}_3)_2\text{Cl}_2$ (Q is phenyl). The reaction is typically conducted in the presence of a bis(triphenylphosphine) palladium (II) chloride catalyst and an acid acceptor (such as diethylamine or triethylamine) under an inert gas (argon) atmosphere, by allowing the reaction to proceed at room temperature or by heating in a sealed tube. Thereafter, the trimethylsilyl group is removed by treatment with base, such as potassium carbonate, and the resulting ethynyl compounds of Formula 14 and 15 are coupled with the reagent $\text{Z}_1\text{-Y-A-B}$ where Z_1 is halogen. In other words, the phenyl or heteroaryl substituent is attached to the 6- or 7-ethynyl-1,2,3,4-tetrahydroquinoline derivative by reacting the latter with a halogen substituted phenyl or heteroaromatic compound of the formula $\text{Z}_1\text{-Y-A-B}$, in which the phenyl or heteroaromatic nucleus (Y) either has the desired substituent [A-B] or wherein the actual substituent A-B can be readily converted to the desired substituent by means of organic reactions well known in the art. The coupling reaction is affected directly in the presence of cuprous iodide, a suitable catalyst, typically of the formula $\text{Pd}(\text{PQ}_3)\text{Cl}_2$ and an acid acceptor, such as triethylamine, at room temperature or by heating in a sealed tube under an inert gas (argon) atmosphere. Alternatively, a metal salt, such as the zinc salt derived from the ethynyl compounds of Formula 14 or 15 can be reacted with the reagent $\text{Z}_1\text{-Y-A-B}$ in the presence of a palladium complex catalyst having the formula $\text{Pd}(\text{PQ}_3)_4$ (Q is phenyl) or similar complex.

The products of the latter coupling reactions are the N-alkylated 2-oxo-1,2,3,4-tetrahydroquinoline

derivatives of Formula 16 and the
O-alkoxylated-1,2,3,4-tetrahydroquinoline derivatives
of Formula 17. Reaction of the compounds of Formula 16
with a thiolating reagent (Lawesson's reagent) produces
5 the 2-thio derivatives of the present invention in
accordance with Formula 18.

The compounds of the present invention shown by
the formulas in Reaction Schemes 1 and 2 can be
converted to further compounds within the scope of the
10 invention by certain transformations which, per se, are
known in the art. Similar synthetic transformations
can be performed on the A-B functionality of the
reagent Z₁-Y-A-B which is used in accordance with
Reaction Scheme 2 for the preparation of the compounds
15 of the invention. These transformations are briefly
mentioned below.

Carboxylic acids are typically esterified by
refluxing the acid in a solution of the appropriate
alcohol in the presence of an acid catalyst such as
20 hydrogen chloride or thionyl chloride. Alternatively,
the carboxylic acid can be condensed with the
appropriate alcohol in the presence of
dicyclohexylcarbodiimide and dimethylaminopyridine.
The ester is recovered and purified by conventional
25 means. Acetals and ketals are readily made by the
method described in March, "Advanced Organic
Chemistry," 2nd Edition, McGraw-Hill Book Company, p
810). Alcohols, aldehydes and ketones all may be
protected by forming respectively, ethers and esters,
30 acetals or ketals by known methods such as those
described in McOmie, Plenum Publishing Press, 1973 and
Protecting Groups, Ed. Greene, John Wiley & Sons, 1981.

A means for making compounds where A is (CH₂)_n (n

is 1 - 5) is to subject the compounds of **Formula 1**, where B is an acid or other function, to homologation, using the well known Arndt-Eistert method of homologation, or other known homologation procedures.

5 Similar homologations (and several of the other herein mentioned synthetic transformations) can be transformed on the reagent $Z_1-Y-A-B$. Compounds of the invention, where A is an alkenyl group having one or more double bonds can be made, for example, by having the requisite

10 number of double bonds incorporated into the $Z_1-Y-A-B$ which is reacted with the ethyne compound or its metal salt, as is described in the reference 5,399,561 patent, or shown in **Reaction Scheme 2**. Generally speaking, such compounds where A is an unsaturated

15 carbon chain can be obtained by synthetic schemes well known to the practicing organic chemist; for example by Wittig and like reactions, or by introduction of a double bond by elimination of halogen from an alpha-halo-carboxylic acid, ester or like carboxaldehyde.

20 Compounds of the invention where the A group has a triple (acetylenic) bond can be made by using the corresponding aryl or heteroaryl aldehyde intermediate. Such intermediate can be obtained by reactions well known in the art, for example, by reaction of a

25 corresponding methyl ketone with strong base, such as lithium diisopropylamide.

The acids and salts derived from compounds of **Formula 1** are readily obtainable from the corresponding esters. Basic saponification with an alkali metal base

30 will provide the acid. For example, an ester of **Formula 1** may be dissolved in a polar solvent such as an alkanol, preferably under an inert atmosphere at room temperature, with about a three molar excess of

base, for example, potassium or lithium hydroxide. The solution is stirred for an extended period of time, between 15 and 20 hours, cooled, acidified and the hydrolysate recovered by conventional means.

5 The amide may be formed by any appropriate amidation means known in the art from the corresponding esters or carboxylic acids. One way to prepare such compounds is to convert an acid to an acid chloride and then treat that compound with ammonium hydroxide or an
10 appropriate amine.

Alcohols are made by converting the corresponding acids to the acid chloride with thionyl chloride or other means (J. March, "Advanced Organic Chemistry", 2nd Edition, McGraw-Hill Book Company), then reducing
15 the acid chloride with sodium borohydride (March, Ibid, pg. 1124), which gives the corresponding alcohols. Alternatively, esters may be reduced with lithium aluminum hydride at reduced temperatures. Alkylating these alcohols with appropriate alkyl halides under
20 Williamson reaction conditions (March, Ibid, pg. 357) gives the corresponding ethers. These alcohols can be converted to esters by reacting them with appropriate acids in the presence of acid catalysts or dicyclohexylcarbodiimide and dimethylaminopyridine.

25 Aldehydes can be prepared from the corresponding primary alcohols using mild oxidizing agents such as pyridinium dichromate in methylene chloride (Corey, E. J., Schmidt, G., Tet. Lett., 399, 1979), or dimethyl sulfoxide/oxalyl chloride in methylene chloride (Omura, K., Swern, D., Tetrahedron, 1978, 34, 1651).
30

Ketones can be prepared from an appropriate aldehyde by treating the aldehyde with an alkyl Grignard reagent or similar reagent followed by

oxidation.

Acetals or ketals can be prepared from the corresponding aldehyde or ketone by the method described in March, Ibid, p 810.

5 Compounds of Formula 1 where B is H can be prepared from the corresponding halogenated aromatic compounds, preferably where the halogen is I.

Specific Examples

10 4,4-Dimethyl-2-oxo-1,2,3,4-tetrahydro-
6[(trimethylsilyl)ethynyl]quinoline (Compound 2)

To a solution of 2.33 g (7.8 mmol) of 4,4-dimethyl-6-bromo-2-oxo-1,2,3,4-tetrahydroquinoline (Compound 1) in 40 ml of triethylamine which was degassed under argon for 15 min in a sealable tube, were added successively 0.368 g (1.96 mmol) of copper(I)iodide, 3.9 ml, (20.5 mmol) of (trimethylsilyl)acetylene, and 1.29 g (1.84 mmol) of bis(triphenylphosphine)palladium(II) chloride. The reaction mixture was degassed for an additional 5 min. The tube was sealed and the reaction was heated at 50 °C for 72 h. Thereafter, the reaction mixture was concentrated in vacuo and the residue was purified by flash chromatography (silica, 10 % ethyl acetate in hexane) to give the title compound as a white solid. PNMR (CDCl₃) δ 7.78 (1H, b), 7.41 (1H, d, J = 1.7 Hz), 7.30 (1H, dd, J = 8.2 Hz, 1.7 Hz), 6.67 (1H, d, J = 8.2 Hz), 2.49 (2H, s), 1.33 (6H, s), 0.26 (9H, s).

25 4,4-Dimethyl-2-oxo-1,2,3,4-tetrahydro-6-
ethynylquinoline (Compound 3)

30 To a solution of 2.64 g (9.7 mmol) of 4,4-dimethyl-2-oxo-1,2,3,4-tetrahydro-6[(trimethylsilyl)ethynyl]quinoline (Compound 2) in 200 ml of methanol was added 0.269 g (1.95 mmol) of K₂CO₃

The reaction was stirred at room temperature for 12 h. The reaction was then concentrated in vacuo and water was added to the residue. The aqueous layer was extracted with methylene chloride (2x). The organic
5 layers were dried (MgSO_4), filtered and concentrated in vacuo to give the title compound as a white solid. PNMR (CDCl_3) δ 8.29 (1H, b), 7.43 (1H, d, $J = 1.8$ Hz), 7.32 (1H, dd, $J = 8.2$ Hz, 1.8 Hz), 6.73 (1H, d, $J = 8.2$ Hz), 3.05 (1H, s), 2.49 (2H, s), 1.33 (6H, s).

10 Ethyl 4-iodobenzoate

To a suspension of 10 g (40.32 mmol) of 4-iodobenzoic acid in 100 ml absolute ethanol was added 2 ml thionyl chloride and the mixture was then heated at reflux for 3 hours. Solvent was removed in vacuo and
15 the residue was dissolved in 100 ml ether. The ether solution was washed with saturated NaHCO_3 and saturated NaCl solutions and dried (MgSO_4). Solvent was then removed in vacuo and the residue kugelrohr distilled (100 degrees C; 0.55 mm) to give the title compound as
20 a colorless oil, PMR (CDCl_3): 1.42 (3H, t, $J = 7$ Hz), 4,4 (2H, q, $J = 7$ Hz), 7.8 (4H).

Ethyl 4-[4,4-dimethyl-2-oxo-1,2,3,4-tetrahydro-6-quinolinyl]ethynyl]benzoate (Compound 4)

To a solution of 1.57 g (7.9 mmol) of
25 4,4-dimethyl-2-oxo-1,2,3,4-tetrahydro-6-ethynylquinoline (Compound 3) and 2.31 g (8.4 mmol) of ethyl 4-iodobenzoate in 40 ml of triethylamine which was degassed under argon for 30 min, were added 0.319 g of CuI (1.7 mmol) and 1.36 g (1.94 mmol) of
30 bis(triphenylphosphine)palladium(II) chloride. The reaction mixture was stirred at room temperature for 4 h. The reaction was then concentrated in vacuo, and the residue was purified by flash chromatography

(silica, 10 % ethyl acetate in hexane) to give the title compound as a solid. PNMR (CDCl₃) δ 8.10 (1H, b), 8.02 (2H, d, J = 8.4 Hz), 7.58 (2H, d, J = 8.4 Hz), 7.49 (1H, d, J = 1.6 Hz), 7.38 (1H, dd, J = 8.2 Hz, 1.6 Hz), 6.77 (1H, d, J = 8.1 Hz), 4.39 (q, J = 7.1 Hz), 2.52 (2H, s), 1.41 (3H, t, J = 7.1 Hz), 1.36 (6H, s).
5 Ethyl 4-[(4,4-dimethyl-2-oxo-1,2,3,4-tetrahydro-1-isopropyl-6-quinolinyl)ethynyl]benzoate (Compound 5) and
10 Ethyl 4-[(4,4-dimethyl-2-isopropoxy-3,4-dihydro-6-quinolinyl)ethynyl]benzoate (Compound 6)

To a solution of 0.10 g (0.30 mmol) of ethyl 4-[(4,4-dimethyl-2-oxo-1,2,3,4-tetrahydro-6-quinolinyl)ethynyl]benzoate (Compound 4) in 2 ml of DMF was added 0.0155 g (0.40 mmol) of sodium hydride
15 (prewashed with hexane), followed by 0.287 ml (3.0 mmol) of 2-iodopropane. The resulting mixture was stirred at 25 °C for 12 h under nitrogen purge. Excess solvent was removed by Kugelrohr distillation, and the residue was subjected to flash chromatography (silica
20 gel, 10% ethyl acetate in hexane) to yield the products as white solids.

Compound 5: PNMR (5, CDCl₃) δ 8.03 (2H, d, J = 8.4 Hz), 7.60 (2H, d, J = 8.4 Hz), 7.46 (1H, d, J = 1.8 Hz), 7.42 (1H, dd, J = 6.5 & 1.8 Hz), 7.13 (1H, d, J =
25 8.4 Hz), 4.72 (1H, m), 4.41 (2H, q, J = 7.1 Hz), 2.45 (2H, s), 1.55 (6H, d, J = 7.0 Hz), 1.42 (3H, t, J = 7.2 Hz), 1.32 (6H, s).

Compound 6: PNMR (6, CDCl₃) δ 8.02 (2H, d, J = 8.4 Hz), 7.59 (2H, d, J = 8.4 Hz), 7.46 (1H, d, J = 1.8 Hz), 7.39 (1H, dd, J = 7.9 & 1.8 Hz), 7.12 (1H, d, J =
30 7.9 Hz), 5.44 (1H, m), 4.39 (2H, q, J = 7.2 Hz), 2.27 (2H, s), 1.44 (3H, t, J = 7.2 Hz), 1.34 (6H, t, J = 6.2 Hz), 1.28 (6H, s).

Ethyl 4-[4,4-dimethyl-2-thio-1,2,3,4-tetrahydro-1-iso-propyl-6-quinolinyl)ethynyl]benzoate (Compound 7)

To a solution of 0.186 g (0.51 mmol) of ethyl 4-
[(4,4-dimethyl-2-oxo-1,2,3,4-tetrahydro-(1-iso-propyl-
5 6-quinolinyl)ethynyl]benzoate (Compound 5) in 5 ml of
dry benzene was added 0.232 g (0.60 mmol) of Lawesson's
reagent. The resulting mixture was refluxed for 3 h
and filtered. The filtrate was concentrated in vacuo
to an oil. Purification by flash chromatography
10 (silica gel, 10% ethyl acetate in hexane) yielded the
title compound as a yellow solid.

PNMR (CDCl₃) δ 8.05 (2H, d, J = 8.4 Hz), 7.61 (2H, d, J
= 8.4 Hz), 7.49 (1H, d, J = 1.9 Hz), 7.44 (1H, dd, J =
6.7 & 1.9 Hz), 7.35 (1H, d, J = 8.5 Hz), 6.26 (1H, m),
15 4.41 (2H, q, J = 7.1 Hz), 3.01 (2H, s), 1.54 (6H, d, J
= 7.1 Hz), 1.43 (3H, t, J = 7.2 Hz), 1.27 (6H, s).

Ethyl 4-[(4,4-dimethyl-2-thio-1,2,3,4-tetrahydro-6-quinolinyl)ethynyl]benzoate (Compound 8)

To a solution of 0.285 g (0.80 mmol) of ethyl 4-
20 [(4,4-dimethyl-2-oxo-1,2,3,4-tetrahydro-6-quinolinyl)ethynyl]benzoate (Compound 4) in benzene (15
ml) was added 0.398 g (1.0 mmol) of Lawesson's reagent.
The resulting mixture was refluxed for 3 h and
filtered. The filtrate was concentrated in vacuo to an
25 oil. Purification by flash chromatography (silica gel,
25% ethyl acetate in hexane) yielded the title compound
as a yellow solid.

PNMR (CDCl₃) δ 8.03 (2H, d, J = 8.4 Hz), 7.51 (2H, d, J
= 8.4 Hz), 7.42 (1H, dd, J = 8.2 Hz, J = 1.6 Hz), 6.98
30 (1H, d, J = 8.2 Hz), 4.41 (2H, q, J = 2.9 Hz), 2.95
(2H, s), 1.41 (3H, t, J = 2.9 Hz), 1.33 (6H, s).

Ethyl 4-[(4,4-dimethyl-2-methylthio-3,4-dihydro-6-quinolinyl)ethynyl]benzoate (Compound 9)

To a suspension of 0.0187 g (0.50 mmol) of NaH (washed with hexane three times) in 5 ml of THF was cannulated a solution of 0.172 g (0.50 mmol) of ethyl 4-[(4,4-dimethyl-2-thio-1,2,3,4-tetrahydro-6-quinolinyl)ethynyl]benzoate (Compound 8) in 15 ml of THF. The resulting yellow solution was stirred at room temperature for 1 h. Methyl iodide 0.295 ml (5.0 mmol) was then added dropwise and the solution stirred at room temperature for 1 h. MeOH and water were then added and the mixture was concentrated. Purification by flash chromatography (10 % EtOAc in hexane) gave the title compound as an oil.

PNMR (CDCl₃) δ 8.03 (2H, d, J = 8.4 Hz), 7.59 (2H, d, J = 8.5 Hz), 7.48 (1H, s), 7.44 (1H, dd, J = 6.5 & 1.8 Hz), 7.26 (1H, d, J = 8.0 Hz), 4.37 (2H, q, J = 7.1 Hz), 2.54 (3H, s), 2.34 (2H, s), 1.40 (3H, t, J = 7.1 Hz), 1.25 (6H, s).

Ethyl 4-[(4,4-dimethyl-2-heptylthio-3,4-dihydro-6-quinolinyl)ethynyl]benzoate (Compound 10)

0.025 g (0.694 mmol) of sodium hydride in 2 ml of THF, 0.229 g (0.631 mmol) of ethyl 4-[(4,4-dimethyl-2-thio-1,2,3,4-tetrahydro-6-quinolinyl)ethynyl]benzoate (Compound 8) in 2 ml of THF and 1.03 ml (6.31 mmol) of iodoheptane were reacted substantially in accordance with the procedure used for the preparation of ethyl 4-[(4,4-dimethyl-2-methylthio-3,4-dihydro-6-quinolinyl)ethynyl]benzoate (Compound 9). Purification by flash chromatography (silica gel, 10% ethyl acetate in hexane) yielded the title compound as a yellow solid.

PNMR (CDCl₃) δ 8.04 (2H, d, J = 8.4 Hz), 7.60 (2H, d, J = 8.4 Hz), 7.48 (1H, d, J = 1.78 Hz), 7.44 (1H, dd, J = 6.2 & 1.9 Hz), 7.27 (1H, d, J = 2.9 Hz), 4.42 (2H, q, J

= 7.1 Hz), 3.19 (2H, t, J = 7.4 Hz), 2.34 (2H, s), 1.72 (2H, m), 1.61 (1H, m), 1.42 (3H, t, J = 7.1 Hz), 1.33 (8H, m), 1.27 (6H, s), 0.91 (2H, m).

5 4-[(4,4-Dimethyl-2-iso-propoxy-3,4-dihydro-6-quinolinyl)ethynyl]benzoic acid (Compound 11)

A solution of 0.023 mg (0.06 mmol) of ethyl 4-[(4,4-dimethyl-2-iso-propoxy-3,4-dihydro-6-quinolinyl)ethynyl]benzoate (Compound 6) in 2 ml of THF, 1ml of EtOH, and 2 ml of 1 N LiOH was stirred at room temperature for 1 h. Aqueous work up yielded the title compound as a white solid.

10 ¹H NMR (CD₃COCD₃) δ 8.04 (2H, d, J = 8.5 Hz), 7.65 (2H, d, J = 8.5 Hz), 7.51 (1H, d, J = 1.8 Hz), 7.39 (1H, dd, J = 8.1 & 1.8 Hz), 7.10 (1H, d, J = 8.1 Hz), 5.41 (1H, m), 2.30 (2H, s), 1.31 (6H, t, J = 6.2 Hz), 1.27 (6H, s).

15 Ethyl 4-[(4,4-dimethyl-2-thio-1,2,3,4-tetrahydro-1-iso-propyl-6-quinolinyl)ethynyl]benzoic acid (Compound 12)

Employing the same procedure as for the preparation of 4-[(4,4-dimethyl-2-iso-propoxy-3,4-dihydro-6-quinolinyl)ethynyl]benzoic acid (Compound 11), but using 0.0524 g (0.129 mmol) of ethyl 4-[(4,4-dimethyl-2-thio-1,2,3,4-tetrahydro-(N-isopropyl)-6-quinolinyl)ethynyl]benzoate (Compound 7) in 2 ml of THF, 1 ml of EtOH, and 2 ml of 1N LiOH, the title compound was obtained as a yellow solid.

20 ¹H NMR (CD₃OD) δ 7.93 (2H, d, J = 8.4 Hz), 7.52 (2H, d, J = 8.4 Hz), 7.44 (1H, s), 7.39 (2H, s), 6.12 (1H, m), 2.85 (2H, s), 1.43 (6H, d, J = 7.1 Hz), 1.16 (6H, s).

25 4-[(4,4-Dimethyl-2-thio-1,2,3,4-tetrahydro-6-quinolinyl)ethynyl]benzoic acid (Compound 13)

30 A solution of 0.090 mg (0.20 mmol) of ethyl 4-[(4,4-dimethyl-2-thio-1,2,3,4-tetrahydro-6-quinolinyl)

ethynyl]benzoate (Compound 8) in 2 ml of THF, 1ml of EtOH, and 2 ml of 1 N LiOH was stirred at room temperature for 1 h. Aqueous work up yielded the title compound as a yellow solid.

5 PNMR (CD₃COCD₃) δ 8.07 (2H, d, J = 8.3 Hz), 7.65 (2H, d, J = 8.4 Hz), 7.61 (1H, s), 7.47 (1H, dd, J = 8.2 & 1.7 Hz), 7.24 (1H, d, J = 8.3 Hz), 2.89 (2H, s), 1.31 (6H, s).

10 4-[(4,4-Dimethyl-2-methylthio-3,4-dihydro-6-quinolinyl)ethynyl]benzoic acid (Compound 14)

 A solution of 0.100 g (0.30 mmol) of ethyl 4-[(4,4-dimethyl-2-methylthio-3,4-dihydro-6-quinolinyl)ethynyl]benzoate (Compound 9) in 2 ml of THF, 1 ml of EtOH and 2 ml of 1 N LiOH was stirred at room temperature for 1 h, followed by aqueous work up to yield the title compound as a yellow solid.

15 PNMR (CD₃OD) δ 8.01 (2H, d, J = 8.4 Hz), 7.59 (2H, d, J = 8.4 Hz), 7.52 (1H, d, J = 1.8 Hz), 7.37 (1H, dd, J = 8.2 & 1.8 Hz), 6.90 (1H, d, J = 8.2 Hz), 3.29 (3H, s), 2.47 (2H, s), 1.34 (6H, s).

20 4-[(4,4-Dimethyl-2-heptylthio-3,4-dihydro-6-quinolinyl)ethynyl]benzoic acid (Compound 15)

 0.0647 g (0.140 mmol) of ethyl 4-[(4,4-dimethyl-2-heptylthio-3,4-dihydro-6-quinolinyl)ethynyl]benzoate (Compound 10) in 2 ml of THF, 1 ml of EtOH was reacted with 2 ml of 1 N LiOH substantially in accordance with the procedure used for the preparation of 4-[(4,4-dimethyl-2-iso-propoxy-3,4-dihydro-6-quinolinyl)ethynyl]benzoic acid (Compound 11).

30 Purification by recrystallization in acetonitrile yielded the title compound as a yellow powder.

 PNMR (CD₃OD) δ 7.90 (2H, d, J = 8.4 Hz), 7.47 (2H, d, J = 8.4 Hz), 7.38 (1H, s), 7.29 (1H, dd, J = 6.2 & 1.8

Hz), 7.09 (1H, d, J = 8.0 Hz), 3.05 (2H, t, J = 7.3 Hz), 2.24 (2H, s), 2.34 (2H, s), 1.60 (2H, m), 1.22 (9H, m), 1.13 (6H, s), 0.79 (3H, m).

N-3,3-Dimethylacryloyl-3-bromoaniline (Compound 17)

5 To a suspension of NaH (4.15 g, 173 mmol, 60% in oil) in 50 ml of THF was cannulated a solution of 20.322 g (118 mmol) of 3-bromoaniline in 50 ml of THF. The resulting mixture was stirred at 0 °C for 45 min and warmed to room temperature over a period of 15 min.
10 To this solution was added through cannulation 13.123 g (173 mmol) of 3,3-dimethylacryloyl chloride. The mixture was stirred at room temperature for 24 h and thereafter slowly poured into ice water. The resulting mixture was extracted with methylene chloride (twice),
15 dried over MgSO₄ and concentrated to yield a solid. The solid was purified by recrystallization in hexane/EtOAc (2:1) to give the title compound as a light brown solid.

PNMR (CDCl₃) δ 7.83 (1H, b), 7.30 (4H, m), 5.68 (1H, s), 2.22 (3H, s), 1.90 (3H, s).

4,4-Dimethyl-2-oxo-1,2,3,4-tetrahydro-7-bromoquinoline (Compound 18)

Into a 500 ml round-bottom flask was placed 13.52 g (101 mmol) of AlCl₃ under nitrogen purge and kept at
25 0 °C. Thereafter, 22.41 g of N-3,3-dimethylacryloyl-3-bromoaniline (Compound 17) in 350 ml CH₂Cl₂ was slowly added by syringe. The reaction mixture was stirred at 0 °C for 72 h, and thereafter slowly quenched with small chunks of ice-cubes and finally with water. The
30 aqueous layer was washed with CH₂Cl₂ and the organic layer was dried over Na₂SO₄. The solvent was evaporated and the residue purified by recrystallization from EtOAc - hexane to give the title

compound as off-white solids.

PNMR (CDCl₃) δ 8.87 (1H, b), 7.23 (1H, d, J = 7.95 Hz), 7.16 (2H, s), 7.0 (1H, s), 2.49 (2H, s), 1.32 (6H, s).

4,4-Dimethyl-2-oxo-1,2,3,4-tetrahydro-7[(trimethylsilyl)ethynyl]quinoline (Compound 19)

2.2398 g (8.8 mmol) of 4,4-dimethyl-2-oxo-1,2,3,4-tetrahydro-7-bromoquinoline (Compound 18), 371 mg (1.9 mmol) of CuI, 1.087 g (1.5 mmol) of Pd(PPh₃)₂Cl₂, 35 ml (0.251 mol) of triethylamine and 4.0 ml (28.0 mmol) of trimethylacetylene were reacted substantially in accordance with the procedure used for the preparation of 4,4-dimethyl-2-oxo-1,2,3,4-tetrahydro-6[(trimethylsilyl)ethynyl]quinoline (Compound 2) to give the title compound as pale orange solids (74%).

PNMR (CDCl₃) δ 7.70 (1H, b), 7.23 (1H, d, J = 7.95 Hz), 7.15 (1H, dd, J = 7.95, 1.5 Hz), 6.84 (1H, d, J = 1.5 Hz), 2.49 (2H, s), 1.32 (6H, s), 0.002 (9H, s).

4,4-Dimethyl-2-oxo-1,2,3,4-tetrahydro-7-ethynylquinoline (Compound 20)

1.77 g (6.5 mmol) of 4,4-dimethyl-2-oxo-1,2,3,4-tetrahydro-7[(trimethylsilyl)ethynyl]quinoline (Compound 19), and 175 mg (1.3 mmol) of K₂CO₃ in 60 ml of methanol were reacted substantially in accordance with the procedure used for the preparation of 4,4-dimethyl-2-oxo-1,2,3,4-tetrahydro-6-ethynylquinoline (Compound 3), to give the title compound as an orange oil. The product was used in the next reaction without further purification.

Ethyl 4-[(4,4-dimethyl-2-oxo-1,2,3,4-tetrahydro-7-quinolinyl)ethynyl]benzoate (Compound 21)

1.29 g (6.5 mmol) of 4,4-dimethyl-2-oxo-1,2,3,4-tetrahydro-7-ethynylquinoline (Compound 20), 290 mg (1.5 mmol) of CuI, 1.14 g (1.6 mmol) of

$\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, 65 ml (0.467 mol) of triethylamine and 4.25 g (15.4 mmol) of ethyl 4-iodobenzoate were reacted substantially in accordance with the procedure used for the preparation of ethyl

- 5 4-[(4,4-dimethyl-2-oxo-1,2,3,4-tetrahydro-6-quinolinyl)ethynyl]benzoate (Compound 4) to give the title compound as white solids.

PNMR (CDCl_3) δ 8.10 (1H, b), 8.02 (2H, d, $J = 8.4$ Hz), 7.59 (2H, d, $J = 8.4$ Hz), 7.37 (1H, d, $J = 8.0$ Hz),
10 7.23 (1H, dd, $J = 8.0$ Hz, 1.6 Hz), 7.05 (1H, d, $J = 1.6$ Hz), 4.37 (q, $J = 7.1$ Hz), 2.46 (2H, s), 1.39 (3H, t, $J = 7.1$ Hz), 1.32 (6H, s).

Ethyl 4-[(4,4-dimethyl-2-thio-1,2,3,4-tetrahydro-7-quinolinyl)ethynyl]benzoate (Compound 22)

- 15 To a suspension of (0.51 g, 1.47 mmol) of ethyl [(4,4-dimethyl-2-oxo-1,2,3,4-tetrahydro-7-quinolinyl)-ethynyl]-4-benzoate (Compound 21) in 15 ml of benzene was added 0.54 g (1.3 mmol) of Lawesson's Reagent and the mixture was refluxed for 30 min. by which time TLC
20 (30% EtOAc in hexane) indicated complete disappearance of Compound 21. The mixture was then concentrated and purified by flash chromatography (30% EtOAc in hexane) under nitrogen. The title compound crystallized from the solvent in which it had been eluted, and was
25 collected by filtration as pale yellow crystals.

PNMR (CD_3OD) δ 8.02 (2H, d, $J = 8.3$ Hz), 7.60 (2H, d, $J = 8.5$ Hz), 7.41 (1H, d, $J = 8.0$ Hz), 7.30 (1H, dd, $J = 8.2$ & 1.6 Hz), 7.17 (1H, d, $J = 1.6$ Hz), 4.37 (2H, q, $J = 7.1$ Hz), 2.86 (2H, s), 1.39 (3H, t, $J = 7.1$ Hz), 1.27
30 (6H, s).

Ethyl 4-[(4,4-dimethyl-2-methylthio-3,4-dihydro-7-quinolinyl)ethynyl]benzoate (Compound 23)

To a suspension of 0.037 g (1.5 mmol) of NaH

(hexane washed 3x) in 5 ml of THF was cannulated a solution of 0.24 g (0.66 mmol) of ethyl 4-[(4,4-dimethyl-2-thio-1,2,3,4-tetrahydro-7-quinolinyl)ethynyl]benzoate (Compound 22) in 15 ml of THF. The resulting yellow solution was stirred at room temperature for 1 h. Methyl iodide 0.46 g (0.20 ml, 3.2 mmol) was then added dropwise and the solution stirred at room temperature for 1 h. MeOH and water were then added and the mixture concentrated by evaporation. Purification by flash chromatography (10 % EtOAc in hexane) gave the title compound as an oil. PNMR (CDCl₃) δ 8.02 (2H, d, J = 8.3 Hz), 7.57 (2H, d, J = 8.3 Hz), 7.48 (1H, d, J = 1.6 Hz), 7.31 (1H, dd, J = 7.9 & 1.7 Hz), 7.26 (1H, d, J = 7.9 Hz), 4.39 (2H, q, J = 7.1 Hz), 2.53 (3H, s), 2.34 (2H, s), 1.41 (3H, t, J = 7.1 Hz), 1.24 (6H, s).

4,4-Dimethyl-2-oxo-1,2,3,4-tetrahydro-1-iso-propyl-7-bromoquinoline (Compound 24) and 4,4-Dimethyl-2-iso-propoxy-3,4-dihydro-7-bromoquinoline (Compound 25)

To a suspension of 0.034 g (14 mmol) of sodium hydride in 5.0 ml of dimethylformamide stirring at 0 °C under argon was cannulated a solution of 1.34 g (5.3 mmol) of 4,4-dimethyl-2-oxo-1,2,3,4-tetrahydro-7-bromoquinoline (Compound 18) in 10 ml of dimethylformamide. The resulting mixture was stirred while allowed to come to room temperature over a course of 2 h. 7.6 g (4.5 ml, 45 mmol) of isopropyl iodide was then added and the resulting solution stirred at room temperature for 96 h. Then the reaction mixture was cooled to 0 °C, quenched with water and extracted with methylene chloride (2x). The organic layers were dried (MgSO₄), filtered and concentrated in vacuo. The resulting crude product was purified using flash

chromatography to give the separated title compounds 24 and 25 as clear oils.

Compound 24: PNMR (24 CDCl₃) δ 1.28 (6H, s), 1.53 (6H, d, J = 6.0 Hz), 2.40 (2H, s), 4.61 (1H, p, J = 6.0 Hz), 7.12 (1H, d, J = 8.6 Hz), 7.18 (1H, dd, J = 2.1 & 8.6 Hz), 7.24 (1H, d, J = 2.1 Hz). Compound 25: PNMR (25, CDCl₃) δ 1.23 (6H, s), 1.35 (6H, d, J = 6.0 Hz), 2.22 (2H, s), 5.39 (1H, p, J = 6.0 Hz), 7.12 (1H, d, J = 8.4 Hz), 7.18 (1H, dd, J = 1.8 & 8.4 Hz), 7.30 (1H, d, J = 1.8 Hz).

4,4-Dimethyl-2-iso-propoxy-3,4-dihydro-(7-(trimethylsilyl)ethynyl)quinoline (Compound 26)

To a solution of 0.196 g (0.66 mmol) of 4,4-dimethyl-2-iso-propoxy-1,2,3,4-tetrahydro-7-bromoquinoline (Compound 25) in 3.0 ml of diethylamine which was degassed under argon for 15 min in a sealable tube, were added successively 0.049 g (0.26 mmol) of copper(I) iodide, (2.5 ml, 1.8 mmol) of (trimethylsilyl)acetylene, and 0.152 g (0.22 mmol) of bis(triphenylphosphine)palladium(II) chloride. The reaction mixture was degassed for an additional 5 min, the tube sealed and the reaction was heated at 50 °C for 96 h. The reaction mixture was then concentrated in vacuo. Purification by flash chromatography (silica, 100 % hexane) gave the title compound as an oil.

PNMR (CDCl₃) δ 0.23 (9H, s), 1.23 (6H, s), 1.54 (6H, d, J = 6.3 Hz), 2.23 (2H, s), 5.40 (1H, p, J = 6.3 Hz), 7.17 (2H, s), 7.33 (1H, s).

4,4-Dimethyl-2-iso-propoxy-3,4-dihydro-7-ethynylquinoline (Compound 27)

To a solution of 0.14 g (0.45 mmol) of 4,4-dimethyl-2-iso-propoxy-1,2,3,4-tetrahydro-7-

[(trimethylsilyl)ethynyl]quinoline (Compound 26) in 2.5 ml of methanol was added 0.10 g (0.72 mmol) of potassium carbonate. The reaction mixture was then stirred at room temperature for 2.5 h. The reaction mixture was then concentrated in vacuo and the resulting oil was dissolved in water and extracted with methylene chloride (2x). The organic layers were dried (MgSO₄), filtered and concentrated in vacuo to give the title compound as an oil. This compound was used for the next reaction without further purification.

Ethyl 4-[(4,4-dimethyl-2-isopropoxy-3,4-dihydro-7-quinolinyl)ethynyl]benzoate (Compound 28)

To a solution of 0.097 g (0.40 mmol) of 4,4-dimethyl-2-isopropoxy-1,2,3,4-tetrahydro-7-ethynylquinoline (Compound 27) and 1.16 g (0.75 ml, 4.2 mmol) of ethyl 4-iodobenzoate in 3.0 ml of diethylamine which was degassed under argon for 15 min, was added 0.043 g (0.23 mmol) of copper(I) iodide and then 0.064 g (0.09 mmol) of bis(triphenylphosphine)palladium(II) chloride. The reaction was stirred at room temperature for 16 h. The reaction mixture was then concentrated. Purification by flash chromatography (1.5 % EtOAc in hexane) gave the title compound as an oil.

¹H NMR (CDCl₃) δ 8.00 (2H, d, J = 8.2 Hz), 7.54 (2H, d, J = 8.1 Hz), 7.32 (1H, s), 7.23 (2H, s), 5.40 (1H, p, J = 6.3 Hz), 4.37 (2H, q, J = 7.1 Hz), 2.24 (2H, s), 1.39 (3H, t, J = 7.1 Hz), 1.32 (6H, d, J = 6.2 Hz), 1.24 (6H, s).

4,4-Dimethyl-2-oxo-1,2,3,4-tetrahydro-1-iso-propyl-7-[(trimethylsilyl)ethynyl]quinoline (Compound 29)

To a solution of 0.40 g (1.36 mmol) of 4,4-dimethyl-2-oxo-1,2,3,4-tetrahydro-1-iso-propyl-7-bromoquinoline (Compound 24) in 5.0 ml of triethylamine

which was degassed under argon for 15 min in a sealable tube, were added successively 0.069 g (0.36 mmol) of copper(I)iodide, (1.0 ml, 7.1 mmol) of (trimethylsilyl)acetylene, and 0.147 g (0.21 mmol) of bis(triphenylphosphine)palladium(II) chloride. The reaction mixture was degassed for an additional 5 min. The tube was sealed and the reaction mixture was heated at 50 °C for 72 h. The reaction mixture was concentrated in vacuo. Purification by flash chromatography (silica, 10 % ethyl acetate in hexane) gave the title compound as an oil. ¹H NMR (CDCl₃) δ 0.25 (9H, s), 1.26 (6H, s), 1.54 (6H, d, J = 7.1 Hz), 2.39 (2H, s), 4.60 (1H, p, J = 7.1 Hz), 7.17 (3H, m).

4,4-Dimethyl-2-oxo-1,2,3,4-tetrahydro-1-iso-propyl-7-ethynylquinoline (Compound 30)

To a solution of 4,4-dimethyl-2-oxo-1,2,3,4-tetrahydro-1-isopropyl-7-[(trimethylsilyl)ethynyl]quinoline (Compound 29) in 7.0 ml of methanol was added potassium carbonate. The mixture was stirred at room temperature for 10 h. The reaction mixture was then concentrated in vacuo and the resulting oil was dissolved in water, and extracted using methylene chloride (2x). The organic layers were dried (MgSO₄), filtered and concentrated in vacuo to give the title compound as an oil. ¹H NMR (CDCl₃) δ 1.28 (6H, s), 1.54 (6H, d, J = 7.0 Hz), 2.41 (2H, s), 3.07 (1H, s), 4.65 (1H, p, J = 7.0 Hz), 7.21 (3H, m).

Ethyl 4-[(4,4-dimethyl-2-oxo-1,2,3,4-tetrahydro-1-iso-propyl-7-quinolinyl)ethynyl]benzoate (Compound 31)

To a solution of 0.282 g (1.17 mmol) of 4,4-dimethyl-2-oxo-1,2,3,4-tetrahydro-1-iso-propyl-7-ethynyl quinoline (Compound 30) and 0.52 g (1.9 mmol)

of ethyl 4-iodobenzoate in 2.5 ml of diethylamine which was degassed under argon for 30 min, was added 0.049 g (0.26 mmol) of copper(I) iodide and then 0.159 g (0.23 mmol) of bis(triphenylphosphine)palladium(II) chloride. The reaction was stirred at room temperature for 4 h. The reaction mixture was then concentrated in vacuo. Purification by flash chromatography (silica, 10 % ethyl acetate in hexane) gave the title compound as a solid.

PNMR (CDCl₃) δ 1.30 (6H, s), 1.41 (3H, t, J = 7.1 Hz), 1.59 (6H, d, J = 7.0 Hz), 2.44 (2H, s), 4.39 (2H, q, J = 7.1 Hz), 5.32 (1H, p, J = 7.0 Hz), 7.27 (3H, overlapping), 7.60 (2H, d, J = 8.4 Hz), 8.04 (2H, d, J = 8.4 Hz).

Ethyl 4-[(4,4-dimethyl-2-thio-1,2,3,4-tetrahydro-1-isopropyl-7-quinolinyl)ethynyl]benzoate (Compound 32)

To a suspension of 0.168 g (0.43 mmol) of ethyl 4-[(4,4-dimethyl-2-oxo-1,2,3,4-tetrahydro-1-isopropyl-7-quinolinyl)ethynyl]benzoate (Compound 31) in 5 ml of benzene was added 0.175 g (0.43 mmol) of Lawesson's reagent and the mixture was refluxed for 24 h. The mixture was then concentrated and purified by flash chromatography (5% EtOAc in hexane) under nitrogen to give the title compound as a pale yellow solid.

PNMR (CD₃OD) δ 8.01 (2H, d, J = 8.2 Hz), 7.62 (2H, d, J = 8.3 Hz), 7.52 (1H, s), 7.38 (2H, 2 x d, J = 8.1 Hz), 6.16 (1H, p, J = 7.1 Hz), 4.36 (2H, q, J = 7.1 Hz), 2.91 (2H, s), 1.53 (6H, d, J = 7.1 Hz), 1.38 (3H, t, J = 7.1 Hz), 1.22 (6H, s).

4-[(4,4-Dimethyl-2-thio-1,2,3,4-tetrahydro-7-quinolinyl)ethynyl]benzoic acid (Compound 33)

To a solution of 0.121 g (0.33 mmol) of ethyl 4-[(4,4-dimethyl-2-thio-1,2,3,4-tetrahydro-7-

quinolinyl)ethynyl]benzoate (Compound 22) in 3.0 ml of tetrahydrofuran was added 1.0 ml (1.0 mmol) of 1.0M aqueous LiOH. The resulting solution was stirred at room temperature for 24 h. The reaction was then concentrated, water was added to the solid residue and the resulting aqueous layer was then acidified to pH=1 with 10% HCl, and extracted using diethyl ether (2x). The organic layers were dried with MgSO₄, filtered and concentrated to yield a residue which was washed with warm acetone to give the title compound as a solid.

PNMR (CD₃OD) δ 8.01 (2H, d, J = 8.3 Hz), 7.58 (2H, d, J = 8.3 Hz), 7.38 (1H, d, J = 8.0 Hz), 7.23 (1H, dd, J = 7.9 & 1.6 Hz), 7.05 (1H, d, J = 1.6 Hz), 2.46 (2H, s), 1.32 (6H, s).

15 4-[(4,4-Dimethyl-2-methylthio-3,4-dihydro-7-quinolinyl)ethynyl]benzoic acid (Compound 34)

To a solution of 0.068 g (0.18 mmol) of ethyl 4-[(4,4-dimethyl-2-methylthio-3,4-dihydro-7-quinolinyl)ethynyl]benzoate (Compound 23) in 3.0 ml of tetrahydrofuran was added 1.0 ml (1.2 mmol) of 1.2M aqueous LiOH. The resulting solution was stirred at room temperature for 4 h and thereafter heated at 40-55 °C for 3 h. The reaction mixture was then concentrated and water was added to the residue. The resulting aqueous layer was acidified to pH=1 with 10% HCl, and extracted using diethyl ether (2x). The organic layers were dried (MgSO₄), filtered and concentrated to give the title compound as a solid.

PNMR (CDCl₃) δ 8.09 (2H, d, J = 8.4 Hz), 7.61 (2H, d, J = 8.4 Hz), 7.54 (1H, s), 7.32 (2H, 2x d, J = 8.6 Hz), 2.57 (3H, s), 2.37 (2H, s), 1.22 (6H, s).

30 4-[(4,4-Dimethyl-2-isopropoxy-3,4-dihydro-7-quinolinyl)ethynyl]benzoic acid (Compound 35)

To a solution of 0.0586 g (0.15 mmol) of 4,4-dimethyl-2-iso-propoxy-1,2,3,4-tetrahydro-7-ethynylquinoline (Compound 27) in 3.0 ml of tetrahydrofuran were added 1.0 ml (1.1mmol) of 1.1M aqueous LiOH and 1.0 ml of methanol. The resulting solution was stirred at room temperature for 2 h. The reaction mixture was then concentrated and water was added to the residue. The aqueous layer was acidified to pH=1 with 10% HCl, and extracted with diethyl ether (2x). The organic layers were dried (MgSO₄), filtered and concentrated to give the title compound as a solid. PNMR (DMSO) δ 7.96 (2H, d, J = 8.4 Hz), 7.65 (2H, d, J = 8.4 Hz), 7.36 (1H, d, J = 7.9 Hz), 7.28 (1H, dd, J = 1.8 & 8.0 Hz), 7.19 (1H, d, J = 1.6 Hz), 5.32 (1H, p, J = 6.2 Hz), 2.29 (2H, s), 1.29 (6H, d, J = 6.2 Hz), 1.19 (6H, s).

4-[4,4-Dimethyl-2-thio-1,2,3,4-tetrahydro-1-iso-propyl-7-quinolinyl)ethynyl]benzoic acid (Compound 36)

To a solution of 0.115 g (0.28 mmol) of ethyl 4-[(4,4-dimethyl-2-thio-1,2,3,4-tetrahydro-1-iso-propyl-7-quinolinyl)ethynyl]benzoate (Compound 32) in 7.0 ml of tetrahydrofuran was added 1.0 ml (1.2 mmol) of 1.2M aqueous LiOH. The resulting solution was stirred at room temperature for 48 h. The reaction mixture was concentrated and water was added to the residue, and the aqueous solution was washed with hexane. The aqueous layer was acidified to pH=1 with 10% HCl, and extracted with (3:1) diethyl ether/methylene chloride (2x). The organic layers were dried (Na₂SO₄), filtered and concentrated to yield the title compound as a solid.

PNMR (CDCl₃) δ 7.96 (2H, d, J = 8.4 Hz), 7.65 (2H, d, J = 8.4 Hz), 7.36 (1H, d, J = 7.9 Hz), 7.28 (1H, dd, J =

1.8 & 8.0 Hz), 7.19 (1H, d, J = 1.6 Hz), 5.32 (1H, p, J = 6.2 Hz), 2.29 (2H, s), 1.29 (6H, d, J = 6.2 Hz), 1.19 (6H, s).

5 Ethyl 4-[(4,4-dimethyl-2-oxo-1,2,3,4-tetrahydro-1-benzyl-6-quinolinyl)ethynyl]benzoate (Compound 37)

NaH (93.6 mg, 2.6 mmol), ethyl 4-(4,4-dimethyl-2-oxo-1,2,3,4-tetrahydro-6-quinolinyl)ethynyl benzoate (Compound 4, 604 mg, 1.7 mmol) and benzyl bromide (2.06 mL, 17 mmol) in 3 mL of DMF were reacted substantially in accordance with the procedure used for the preparation of ethyl 4-[(4,4-dimethyl-2-oxo-1,2,3,4-tetrahydro-(1-iso-propyl-6-quinolinyl)ethynyl]benzoate (Compound 5), to yield the title compound as white solids (744 mg).

15 ¹H NMR δ 8.02 (d, J = 8.5 Hz, 1H), 7.57 (d, J = 8.5 Hz, 1H), 7.49 (d, J = 1.9 Hz, 1H), 7.3 (m, 6H), 6.90 (d, J = 8.5 Hz, 1H), 5.23 (s, 2H), 4.38 (q, J = 7.2 Hz, 2H), 2.68 (s, 2H), 1.41 (t, J = 7.2 Hz, 3H), 1.37 (s, 6H).

20 Ethyl 4-[(4,4-dimethyl-2-oxo-1,2,3,4-tetrahydro-1-heptyl-6-quinolinyl)ethynyl]benzoate (Compound 38)

NaH (98.4 mg, 2.7 mmol), ethyl 4-[(4,4-dimethyl-2-oxo-1,2,3,4-tetrahydro-6-quinolinyl)ethynyl]benzoate (Compound 4, 635 mg, 1.8 mmol) and iodo heptane (2.73 mL, 18 mmol) in 3 mL of DMF were reacted substantially in accordance with the procedure used for the preparation of ethyl 4-[(4,4-dimethyl-2-oxo-1,2,3,4-tetrahydro-1-iso-propyl-6-quinolinyl)ethynyl]benzoate (Compound 5), to give the title compound as white solids.

30 ¹H NMR δ 8.04 (d, J = 8.3 Hz, 1H), 7.60 (d, J = 8.5 Hz, 1H), 7.49 (d, J = 1.9 Hz, 1H), 7.43 (dd, J₁ = 1.9 Hz, J₂ = 8.3 Hz, 1H), 7.00 (d, J = 8.5 Hz, 1H), 4.39 (q, J = 7.2 Hz, 2H), 3.97 (t, J = 7.9 Hz, 2H), 2.52 (s, 2H),

1.6 (m, 2H), 1.41 (t, J = 7.2 Hz, 3H), 1.35 (m, 10H), 1.32 (s, 6H), 0.89 (t, J = 6.7 Hz, 3H).

4-[(4,4-Dimethyl-2-oxo-1,2,3,4-tetrahydro-1-benzyl-6-quinolinyl)ethynyl]benzoic acid (Compound 39)

5 95.6 mg (0.23 mmol) of ethyl 4-[(4,4-dimethyl-2-oxo-1,2,3,4-tetrahydro-1-benzyl-6-quinolinyl)ethynyl]benzoate (Compound 37) in 2 ml of THF, 2 ml of EtOH, and 1 ml of 1N LiOH were reacted substantially in accordance with the procedure used for
10 the preparation of 4-[4,4-dimethyl-2-isopropoxy-1,2,3,4-tetrahydro-6-quinolinyl]ethynyl benzoic acid (Compound 11) to give the title compound as a white solid (131 mg).

15 ¹H NMR δ 8.09 (d, J = 8.5 Hz, 1H), 7.60 (d, J = 8.5 Hz, 1H), 7.30 (m, 6H), 6.91 (d, J = 8.5 Hz, 1H), 5.24 (s, 2H), 2.69 (s, 2H), 1.38 (s, 6H).

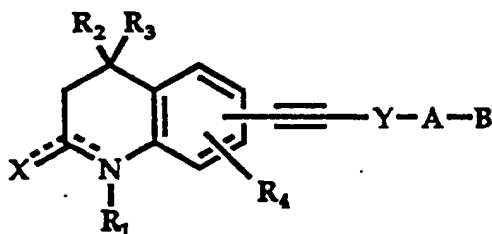
4-[4,4-Dimethyl-2-oxo-1,2,3,4-tetrahydro-1-heptyl-6-quinolinyl]ethynyl]benzoic acid (Compound 40)

20 163 mg (0.39 mmol) of ethyl 4-[(4,4-dimethyl-2-oxo-1,2,3,4-tetrahydro-1-benzyl-6-quinolinyl)ethynyl]benzoate (Compound 37) in 2 ml of THF, 2 ml of EtOH, and 2 ml of 1N LiOH were reacted substantially in accordance with the procedure used for the preparation of 4-[(4,4-dimethyl-2-iso-propoxy-3,4-dihydro-6-quinolinyl)ethynyl]benzoic acid (Compound 11)
25 to give the title compound as a white flaky solid.

30 ¹H NMR δ 8.11 (d, J = 8.3 Hz, 1H), 7.61 (d, J = 8.5 Hz, 1H), 7.49 (d, J = 1.9 Hz, 1H), 7.44 (dd, J₁ = 1.9 Hz, J₂ = 8.3 Hz, 1H), 7.01 (d, J = 8.5 Hz, 1H), 3.98 (t, J = 7.9 Hz, 2H), 2.55 (s, 2H), 1.66 (m, 2H), 1.32 (m, 16H), 0.89 (t, J = 6.7 Hz, 3H).

WHAT IS CLAIMED IS:

1. A compound of the formula



where the dotted lines represent a bond or the absence of a bond;

R_1 is H, lower alkyl of 1 to 10 carbons, lower alkenyl of 2 to 10 carbons, phenyl $C_1 - C_6$ lower alkyl, phenyl $C_2 - C_6$ lower alkenyl, heteroaryl $C_1 - C_6$ lower alkyl, heteroaryl $C_2 - C_6$ lower alkenyl, or R_1 is absent;

X is S, O, R_5S or R_5O where R_5 is lower alkyl of 1 to 10 carbons, lower alkenyl of 2 to 10 carbons, phenyl $C_1 - C_6$ lower alkyl, phenyl $C_2 - C_6$ lower alkenyl, heteroaryl $C_1 - C_6$ lower alkyl, heteroaryl $C_2 - C_6$ lower alkenyl, with the proviso that when R_1 is H then X is S;

R_2 and R_3 are hydrogen, lower alkyl of 1 - 6 carbons, or halogen;

R_4 is hydrogen, lower alkyl of 1 - 6 carbons, halogen, OR_{11} , SR_{11} , $OCOR_{11}$, $SCOR_{11}$, NH_2 , NHR_{11} , $N(R_{11})_2$, $NHCOR_{11}$ or $NR_{11}COR_{11}$;

Y is phenyl or a heteroaryl group selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, imidazolyl and oxazolyl;

A is $(CH_2)_n$ where n is 0-5, lower branched chain alkyl having 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6 carbons and 1 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2 triple bonds;

B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, $COOR_8$, $CONR_9R_{10}$, $-CH_2OH$, CH_2OR_{11} , CH_2OCOR_{11} , CHO, $CH(OR_{12})_2$, $CHOR_{13}O$, $-COR_7$, $CR_7(OR_{12})_2$, or $CR_7OR_{13}O$, where R_7 is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R_8 is an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R_8 is phenyl or lower alkylphenyl, R_9 and R_{10} independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R_{11} is lower alkyl, phenyl or lower alkylphenyl, R_{12} is lower alkyl, and R_{13} is divalent alkyl radical of 2-5 carbons.

2. A compound in accordance with Claim 1 wherein X is S.

3. A compound in accordance with Claim 2 wherein R_1 is H, lower alkyl or benzyl.

4. A compound in accordance with Claim 3 wherein A is $(CH_2)_n$, and B is COOH or a pharmaceutically acceptable salt thereof, $COOR_8$, or $CONR_9R_{10}$.

5. A compound in accordance with Claim 1 wherein X is O.

6. A compound in accordance with Claim 5 wherein R_1 is lower alkyl or benzyl.

7. A compound in accordance with Claim 6 wherein A is $(CH_2)_n$, and B is COOH or a pharmaceutically acceptable salt thereof, $COOR_8$, or $CONR_9R_{10}$.

8. A compound in accordance with Claim 1 wherein

X is OR_5 .

9. A compound in accordance with Claim 8 wherein R_5 is lower alkyl or benzyl.

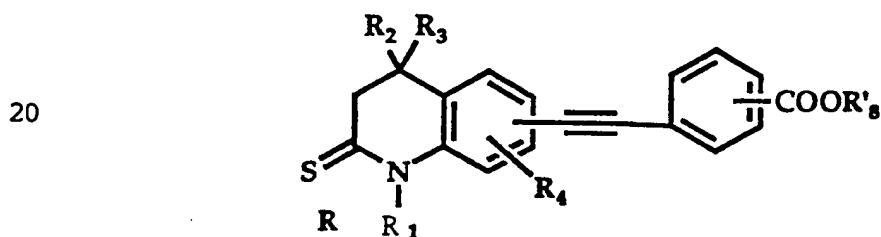
10. A compound in accordance with Claim 9 wherein
5 A is $(CH_2)_n$, and B is COOH or a pharmaceutically acceptable salt thereof, $COOR_8$, or $CONR_9R_{10}$.

11. A compound in accordance with Claim 1 wherein X is SR_5 .

12. A compound in accordance with Claim 11
10 wherein R_5 is lower alkyl or benzyl.

13. A compound in accordance with Claim 12 wherein A is $(CH_2)_n$, and B is COOH or a pharmaceutically acceptable salt thereof, $COOR_8$, or $CONR_9R_{10}$.

14. A compound of the formula



25

where R_1 is H, lower alkyl of 1 to 10 carbons, or phenyl $C_1 - C_6$ lower alkyl;

30 R_2 and R_3 are hydrogen, or lower alkyl of 1 - 6 carbons;

R_4 is hydrogen, lower alkyl of 1 - 6 carbons, or halogen,

and R'_8 is H, an alkyl group of 1 to 10 carbons,

or a cycloalkyl group of 5 to 10 carbons, or R_8 is phenyl or lower alkylphenyl.

15 15. A compound in accordance with Claim 14 wherein R_1 is H, lower alkyl of 1 to 10 carbons, or benzyl.

16. A compound in accordance with Claim 15 wherein R_2 and R_3 are methyl and R_4 is H.

17. A compound in accordance with Claim 16 wherein R'_8 is H, or lower alkyl of 1 to 6 carbons.

10 18. A compound in accordance with Claim 17 wherein the phenyl group is 1,4 (para) substituted.

19. A compound in accordance with Claim 18 which is:

15 (1) ethyl 4-[(4,4-dimethyl-2-thio-1,2,3,4-tetrahydro-1-iso-propyl-6-quinolinyl)ethynyl]benzoate;

(2) ethyl 4-[(4,4-dimethyl-2-thio-1,2,3,4-tetrahydro-6-quinolinyl)ethynyl]benzoate;

20 (3) ethyl 4-[(4,4-dimethyl-2-thio-1,2,3,4-tetrahydro-1-iso-propyl-6-quinolinyl)ethynyl]benzoic acid;

(4) 4-[(4,4-dimethyl-2-thio-1,2,3,4-tetrahydro-6-quinolinyl)ethynyl]benzoic acid;

(5) ethyl 4-[(4,4-dimethyl-2-thio-1,2,3,4-tetrahydro-7-quinolinyl)ethynyl]benzoate;

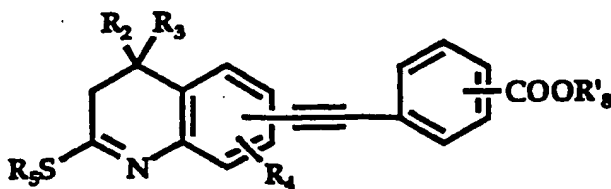
25 (6) ethyl 4-[(4,4-dimethyl-2-thio-1,2,3,4-tetrahydro-1-iso-propyl-7-quinolinyl)ethynyl]benzoate;

(7) 4-[(4,4-dimethyl-2-thio-1,2,3,4-tetrahydro-1-iso-propyl-7-quinolinyl)ethynyl]benzoic acid, and

30 (8) 4-[(4,4-dimethyl-2-thio-1,2,3,4-tetrahydro-1-iso-propyl-7-quinolinyl)ethynyl] benzoic acid.

20. A compound of the formula

5



where R_5 is lower alkyl of 1 to 10 carbons, or
 10 phenyl $C_1 - C_6$ lower alkyl;

R_2 and R_3 are hydrogen, or lower alkyl of 1 - 6 carbons;

R_4 is hydrogen, lower alkyl of 1 - 6 carbons, or halogen,

15 and R'_8 is H, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R_8 is phenyl or lower alkylphenyl.

21. A compound in accordance with Claim 20 wherein R_5 is lower alkyl of 1 to 10 carbons, or
 20 benzyl.

22. A compound in accordance with Claim 21 wherein R_2 and R_3 are methyl and R_4 is H.

23. A compound in accordance with Claim 22 wherein R'_8 is H, or lower alkyl of 1 to 6 carbons.

25 24. A compound in accordance with Claim 23 wherein the phenyl group is 1,4 (para) substituted.

25. A compound in accordance with Claim 24 which is:

(1) ethyl 4-[(4,4-dimethyl-2-methylthio-3,4-dihydro-6-quinolinyl)ethynyl]benzoate;

(2) ethyl 4-[(4,4-dimethyl-2-heptylthio-3,4-dihydro-6-quinolinyl)ethynyl]benzoate;

(3) 4-(4,4-dimethyl-2-methylthio-3,4-dihydro-6-

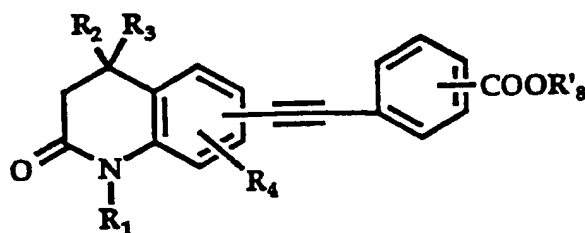
quinolinyl)ethynyl]benzoic acid;

(4) 4-[(4,4-dimethyl-2-heptylthio-3,4-dihydro-6-quinolinyl)ethynyl]benzoic acid;

(5) ethyl 4-[(4,4-dimethyl-2-methylthio-3,4-dihydro-7-quinolinyl)ethynyl]benzoate, and

(6) 4-[(4,4-dimethyl-2-methylthio-3,4-dihydro-7-quinolinyl)ethynyl]benzoic acid.

26. A compound of the formula



where R_1 is lower alkyl of 1 to 10 carbons, or phenyl $C_1 - C_6$ lower alkyl;

R_2 and R_3 are hydrogen, or lower alkyl of 1 - 6 carbons;

R_4 is hydrogen, lower alkyl of 1 - 6 carbons, or halogen,

and R'_8 is H, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R_8 is phenyl or lower alkylphenyl.

27. A compound in accordance with Claim 26 wherein R_1 is H, lower alkyl of 1 to 10 carbons, or benzyl.

28. A compound in accordance with Claim 27 wherein R_2 and R_3 are methyl and R_4 is H.

29. A compound in accordance with Claim 28 wherein R'_8 is H, or lower alkyl of 1 to 6 carbons.

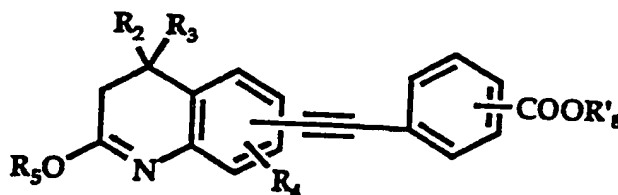
30. A compound in accordance with Claim 29 wherein the phenyl group is 1,4 (para) substituted.

31. A compound in accordance with Claim 30 which is:

- 5 (1) ethyl 4-[(4,4-dimethyl-2-oxo-1,2,3,4-tetrahydro-1-iso-propyl-6-quinolinyl)ethynyl]benzoate;
- (2) ethyl 4-[(4,4-dimethyl-2-oxo-1,2,3,4-tetrahydro-1-iso-propyl-7-quinolinyl)ethynyl]benzoate;
- (3) ethyl 4-[(4,4-dimethyl-2-oxo-1,2,3,4-tetrahydro-1-benzyl-6-quinolinyl)ethynyl]benzoate;
- 10 (4) ethyl 4-[(4,4-dimethyl-2-oxo-1,2,3,4-tetrahydro-1-heptyl-6-quinolinyl)ethynyl]benzoate;
- (5) 4-[(4,4-dimethyl-2-oxo-1,2,3,4-tetrahydro-1-benzyl-6-quinolinyl)ethynyl]benzoic acid, and
- 15 (6) 4-[4,4-dimethyl-2-oxo-1,2,3,4-tetrahydro-1-heptyl-6-quinolinyl)ethynyl]benzoic acid.

32. A compound of the formula

20



25

where R₅ is lower alkyl of 1 to 10 carbons, or phenyl C₁ - C₆ lower alkyl;

30 R₂ and R₃ are hydrogen, or lower alkyl of 1 - 6 carbons;

R₄ is hydrogen, lower alkyl of 1 - 6 carbons, or halogen,

and R'₈ is H, an alkyl group of 1 to 10 carbons,

or a cycloalkyl group of 5 to 10 carbons, or R₈ is phenyl or lower alkylphenyl.

33. A compound in accordance with Claim 32 wherein R₅ is H, lower alkyl of 1 to 10 carbons, or benzyl.

34. A compound in accordance with Claim 33 wherein R₂ and R₃ are methyl and R₄ is H.

35. A compound in accordance with Claim 34 wherein R₈ is H, or lower alkyl of 1 to 6 carbons.

36. A compound in accordance with Claim 35 wherein the phenyl group is 1,4 (para) substituted.

37. A compound in accordance with Claim 36 which is:

- (1) ethyl 4-[(4,4-dimethyl-2-iso-propoxy-3,4-dihydro-6-quinolinyl)ethynyl]benzoate;
- (2) 4-[(4,4-dimethyl-2-iso-propyloxy-3,4-dihydro-6-quinolinyl)ethynyl]benzoic acid;
- (3) ethyl 4-[(4,4-dimethyl-2-iso-propyloxy-3,4-dihydro-7-quinolinyl)ethynyl]benzoate, and
- (4) 4-[(4,4-dimethyl-2-iso-propyloxy-3,4-dihydro-7-quinolinyl)ethynyl]benzoic acid.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/06866

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D215/22 A61K31/47 C07D215/36

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,5 399 561 (ALLERGAN, INC.) 21 March 1995 cited in the application see claims ---	1
A	US,A,5 023 341 (ALLERGAN, INC.) 11 June 1991 cited in the application * see column 35-36: compound 108 * ---	1
A	US,A,5 089 509 (ALLERGAN, INC.) 18 February 1992 cited in the application see claims -----	1



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

6 August 1996

Date of mailing of the international search report

21. 08. 96

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+ 31-70) 340-3016

Authorized officer

Van Bijlen, H

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. Application No

PCT/US 96/06866

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-5399561	21-03-95	US-A- 5278318	11-01-94
		US-A- 5407937	18-04-95
		US-A- 5346915	13-09-94
		US-A- 5346895	13-09-94
		US-A- 5162546	10-11-92
		US-A- 4980369	25-12-90
		US-A- 5272156	21-12-93
		US-A- 5183827	02-02-93
		US-A- 5045551	03-09-91
		AU-B- 1725695	01-08-95
		WO-A- 9518803	13-07-95
		US-A- 5534516	09-07-96
		AU-B- 652830	08-09-94
		AU-B- 1755592	02-11-92
		CA-A- 2105379	27-09-92
		EP-A- 0577737	12-01-94
		JP-T- 6506935	04-08-94
		WO-A- 9217471	15-10-92
		AT-T- 124690	15-07-95
		AU-B- 627356	20-08-92
		AU-B- 6259290	28-03-91
		CA-A- 2023813	20-03-91
		DE-D- 69020672	10-08-95
		DE-T- 69020672	07-03-96
		EP-A- 0419131	27-03-91
		ES-T- 2075162	01-10-95
		JP-A- 3120273	22-05-91
		AT-T- 130297	15-12-95
		AU-B- 627355	20-08-92
		AU-B- 6259190	28-03-91
		CA-A- 2023812	20-03-91
		DE-D- 69023588	21-12-95
		DE-T- 69023588	13-06-96
		EP-A- 0419130	27-03-91
		ES-T- 2079446	16-01-96
		JP-A- 3120274	22-05-91
		AU-B- 648158	14-04-94
		AU-B- 1439592	15-09-92
		CA-A- 2101160	14-08-92
		EP-A- 0571546	01-12-93

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 96/06866

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-5399561		WO-A- 9214725	03-09-92
US-A-5023341	11-06-91	AT-T- 127463	15-09-95
		AU-B- 638275	24-06-93
		AU-B- 6261590	28-03-91
		CA-A- 2023811	20-03-91
		CN-A,B 1050385	03-04-91
		DE-D- 69022152	12-10-95
		DE-T- 69022152	09-05-96
		EG-A- 19293	30-11-94
		EP-A- 0419132	27-03-91
		ES-T- 2076325	01-11-95
		IL-A- 95475	27-11-95
		JP-A- 3167174	19-07-91
		RU-C- 2015969	15-07-94
		US-A- 5053523	01-10-91
		US-A- 5248777	28-09-93
US-A-5089509	18-02-92	US-A- 5348972	20-09-94
		US-A- 5380877	10-01-95
		US-A- 5468879	21-11-95
		US-A- 5354752	11-10-94
		US-A- 5234926	10-08-93
		US-A- 5264578	23-11-93